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THE ROLE OF ISO-IMMUNIZATION IN THE PATHOGENESIS OF ERYTHROBLASTOSIS FETALIS*

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STUDIES on the cause of intra-group transfusion accidents associated with pregnancy have established the importance of the concept of iso-immunization of the mother by blood factors in the fetus transmitted from the father.[1-5] More recently it was found that the same theory of iso-immunization may serve as the basis for a theory on the pathogenesis of erythroblastosis fetalis, the well-described familial hemolytic disease of the newborn.[3, 4, 6]

The data to be presented indicate that erythroblastosis fetalis results from (1) iso-immunization of the mother by dominant hereditary blood factors in the fetus, as evidenced by the production of immune intra-group agglutinins and (2) the subsequent passage of these maternal agglutinins through the placenta and their continuous action on the susceptible fetal blood. In the great majority of the cases the blood factor involved has been shown to be either identical with or related to the Rh (Rhesus) agglutinogen first described by Landsteiner and Wiener with the aid of rabbit sera prepared by injection of Rhesus blood.[7] In other words, the rabbit anti-Rhesus immune sera and the sera of pregnant women suffering from intra-group transfusion accidents gave almost identical agglutination reactions on all human bloods

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tested. Accordingly, a pregnant woman whose blood does not contain the Rh factor (Rh–, occurring in about 15 per cent of the general population) if married to an Rh husband (85 per cent in the random population), may produce anti-Rh agglutinins as a result of immunization with the Rh fetal blood. Should these agglutinins penetrate the placenta in suitable concentration they may serve as the source of the intrauterine hemolysis of fetal blood, the characteristic feature of erythroblastosis fetalis.[4]

The term iso-immunization denotes immunization within the same species, i.e., the individual being immunized and source of the antigenic (immunizing) stimulus belong to the same species. It is obvious that patients receiving repeated blood transfusions may be subjected to iso-immunization. A prerequisite condition is an antigenic difference in the bloods of recipient and donor. In each instance, this difference is expressed by the presence of a particular blood factor in the donor and its absence in the recipient. Although this condition is frequently satisfied in many cases of repeated transfusions, immune agglutinins are rarely produced because many human blood factors which immunize animals are not antigenic in man. An exception to this rule is the Rh factor which has recently been shown to be responsible for transfusion accidents in Rh– recipients who in the course of several transfusions produced anti-Rh agglutinins.[5, 8, 9] In short, the Rh factor is a good antigen for Rh– mothers as well as for Rh– recipients.

Iso-immunization in pregnancy as the cause of the production of atypical agglutinins responsible for an intra-group transfusion accident was suggested by Levine and Stetson[1] in 1939. In this case the patient (Group O), who harbored a dead fetus for two months, was transfused with her husband's blood (Group O) after the delivery of a macerated fetus (October, 1937). This transfusion was followed by an immediate severe reaction resulting in jaundice, anuria, and ultimate recovery. It was later shown that this patient's blood contained an atypical agglutinin which agglutinated about 80 per cent of Group O bloods. As was to have been expected, this agglutinin gradually diminished in titer and entirely disappeared from the blood at the end of one year. In 1940, or three years after the transfusion accident, it could be shown that the patient was Rh– and her husband Rh+. There is still further evidence that the atypical agglutinin in this patient was anti-Rh in its specificity since the same donors selected as compatible* for subsequent uneventful transfusions in 1937 were later (1940) found to be Rh– in tests with a human anti-Rh serum.

Recent studies have shown that intra-group transfusion accidents previously reported in the literature[5] and additional cases recently observed by Levine, Katzin, and Burnham,[2, 3, 10] occurred frequently in conditions associated with pregnancy. It is characteristic of this group of cases that the accident occurs at the first transfusion. Accordingly, the immune agglutinin which must have been present prior to the transfusion but could not be demonstrated with the usual cross-matching procedure, was probably induced by the pregnancy.

*These tests were carried out by Dr. E. M. Katzin.

The atypical agglutinins in some of these cases were shown to have the unusual property of greater activity at 37° C. than at 20° C. (low room temperature). For this reason, the term "warm agglutinins" was applied to these antibodies.[10] This observation offers a possible explanation for the frequent failure of the cross-matching tests to detect this form of intra-group incompatibility. It is therefore recommended that in performing the compatibility test, the patient's serum and donor's blood cell suspension be incubated at 37° C. for thirty minutes before the mixture is centrifuged (one minute at 500 r.p.m.) for sedimentation and subsequent resuspension.[4, 11, 12]

The relationship of iso-immunization and certain pathologic states in the pregnant woman or in the fetus was pointed out by Levine and Katzin.[2] In an analysis of 12 intra-group transfusion accidents associated with pregnancy in which atypical agglutinins were demonstrated, these authors observed a high incidence of toxemia, spontaneous abortions and miscarriages, and stillbirths in the past obstetric histories. Accordingly, it was assumed that "there does appear to be a correlation of the complications with the incidence of atypical agglutinins, and one can speculate as to their relationship."

This observation made it possible to enlarge the source of the material to be studied instead of limiting it to the comparatively rare transfusion accidents in pregnancy.

Shortly thereafter, one of us (L. B.) observed a patient who suffered from a severe transfusion accident following the delivery of an infant in whom a diagnosis of erythroblastosis fetalis was established. The obstetric history in this case (R. C.)* and in still another case (J. L.) not transfused, were so striking as to suggest a theoretical basis for the pathogenesis of erythroblastosis fetalis.[3, 4] One of these mothers (R. C.) had three pregnancies, the first and third of which resulted in infants with erythroblastosis fetalis and the second pregnancy terminated in a macerated fetus. In the other case (J. L.), there had been 10 pregnancies, the first of which resulted in a normal infant; there were 3 spontaneous abortions and the remaining 6 pregnancies resulted in infants who survived one to three days. In at least 3 of these neonatal deaths there was sufficient evidence to support a diagnosis of erythroblastosis fetalis. This woman's blood was tested in the eighth month of her eleventh pregnancy. Since atypical agglutinins were already present, it was anticipated that the baby to be born would be affected. Actually, the infant suffered from anemia of the newborn, one of the several manifestations of erythroblastosis fetalis.

The two cases mentioned were among the seven patients with 37 pregnancies which formed the basis for the preliminary observation that the pathogenesis of erythroblastosis fetalis depends on iso-immunization of the mother by the fetus. The findings in these 37 pregnancies are reproduced in Table I.

*Another patient of Dr. Burnham (G. B.) who died from a transfusion anuria following the delivery of an infant with fetal hydrops, was mentioned in previous papers.[2, 3, 10] These two cases were the first to show the relationship of intra-group transfusion accidents and erythroblastosis fetalis. A more detailed discussion is given in a paper by Burnham.[13]

TABLE I. OUTCOME OF 37 PREGNANCIES IN 7 PATIENTS

(Modified After Levine, Katzin and Burnham[3])

Normal babies	10
Babies with erythroblastosis	7
Neonatal deaths	3
Stillbirths	5
Abortions or miscarriages (at least 6 spontaneous)	10
No data available	2

In 6 of these 7 women in whose blood atypical agglutinins were demonstrated, there were indications that the specificity of the antibodies corresponded to the anti-Rh. Obviously, the blood cells of these women did not contain the Rh factor and were therefore Rh–. These considerations suggested a statistical study of the bloods of women known to have given birth to infants in whom a diagnosis of erythroblastosis fetalis was established. If iso-immunization with the Rh factor plays a significant role in the pathogenesis of this disease, one should expect to find (1) a high incidence of Rh– reactions in this group of selected mothers and (2) a high incidence of anti-Rh agglutinins in their sera.

Whenever possible, the bloods of the fathers and the affected children were also tested, for, if the iso-immunization theory is correct, then 100 per cent of the fathers and the affected children in the series of Rh– mothers should be Rh+.

In each case, suspensions of red blood cells were tested with potent human anti-Rh agglutinins to determine whether the blood was Rh– or Rh+. Since the Rh factor is a constant immutable hereditary property of the red blood cells, it is obvious that such tests could be made at any interval after the last delivery of an affected infant.

The presence or absence of atypical agglutinins was determined by testing each serum with blood suspensions of at least 10 individuals of Group O, of which at least 1 was Rh–. It is obvious that the possibility of demonstrating atypical agglutinins was better if the serum was studied soon after birth of the affected infant.

EXPERIMENTAL

Selection of the Cases.—This study is based chiefly on blood tests of 153 mothers who delivered one or more infants suffering from one of three clinical forms of erythroblastosis fetalis, i.e., fetal hydrops, icterus gravis, or anemia of the newborn. Of these, 115 were under observation either by one of the authors or by other collaborators.* Thirty-eight mothers were referred to us from several sources mainly outside of the metropolitan area of New York. The diagnosis in the affected infants in the latter group could be accepted on the basis of a history submitted by the physicians referring the case. In each case, some or all characteristic features were present, such as a significant obstetrical history of previous miscarriages or stillbirths, or infants with erythroblastosis fetalis—and the accepted diagnostic criteria such as severe icterus at or shortly after birth, enlarged liver and spleen, excess of normoblasts

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in the peripheral circulation, progressive anemia, and in fatal cases post-mortem findings of extramedullary hematopoiesis.

In addition to the 153 mothers of infants in whom a diagnosis of erythroblastosis fetalis was established, data will be presented below (p. 933) in a smaller number of women whose pregnancies terminated in habitual abortion, miscarriages, stillbirths, or macerated fetuses.

Technique of the Agglutination Tests.—Diagnosis of Rh+ and Rh– blood: One or more drops of anti-Rh serum are mixed in small test tubes (75 × 10 mm.) with 2 drops of a washed 1 per cent to 2 per cent cell suspension (this corresponds to a suspension made by adding one drop of whole blood to 4 c.c. saline). The cell suspension is preferably prepared from the clot.

The tubes are shaken and incubated in a water-bath at 37° C. for one hour, at the end of which period each tube is properly identified and all tubes are centrifuged at low speed (500 r.p.m.) for one minute. After replacing the tubes in the rack, the sedimented cells are resuspended by gentle shaking and readings are recorded. Those mixtures in which no gross agglutination is visible are examined microscopically (low magnification) by withdrawing with the aid of a glass rod some of the mixture onto a slide. Bloods showing no agglutination are Rh–.

Detection of Anti-Rh in Human Sera.—Two drops of the serum to be tested are added to each of 10 small test tubes and each tube receives two drops of washed cell suspension of ten different Group O bloods. As a rule, at least one Rh– blood is included. The tests are incubated at 37° C. for one hour, and readings are made after centrifuging the tests and resuspension of the sediments as indicated above.

All cases were tested with one or more of three potent anti-Rh sera. Since the first serum employed (December, 1940) was of Group A (patient M. F.) all bloods of Groups O and A could be tested directly. In order to test bloods of Groups B and AB, it was necessary to treat this serum with an Rh– blood of Group B, in order to remove the normal iso-agglutinin anti-B. In April, 1941, the second potent anti-Rh serum was found (Patient E. B.). Since this serum belonged to Group AB, it could be used directly on bloods of all groups. In May, 1941, the third anti-Rh serum (M. S.) of Group O became available.

In the latter part of these studies, bloods of all groups could be tested in parallel with three anti-Rh sera. This became possible because of the availability of Witebsky's group specific soluble Substances A and B,[15]* the addition of which in small quantities inhibited the action of agglutinin anti-A and anti-B without affecting the activity of anti-Rh.

In any event, each of the three sera gave distinct agglutination reactions so that there was never any doubt as to the diagnosis of Rh+ or Rh–, in any blood tested with a particular serum.

A brief obstetric history of these patients is given below:

1. *M. F. (Group A):* A patient of Dr. P. Vogel had 7 pregnancies of which 6 were full term and one terminated at six months. A diagnosis of erythroblastosis fetalis was made in the last two infants, the most recent one in December, 1940. Serum obtained several weeks post-partum contained potent anti-Rh agglutinins. The agglutinins remained very active though they were somewhat weaker in the blood specimen drawn in May, 1941.

*Supplied by courtesy of Eli Lilly & Co.

2. *E. B. (Group AB):* A patient of Dr. Freed had two full-term pregnancies. The first infant was very pale at birth and survived but one and one-half hours. No other data were available. The second infant, born April, 1941, showed classical symptoms of congenital anemia.

3. *M. S. (Group O):* A patient of Dr. Paul delivered a normal infant in 1931; this pregnancy was followed by a long interval of sterility. The second pregnancy (April, 1941) resulted in an infant suffering from icterus gravis.

Specificities of the Anti-Rh sera, M. F., E. B., and M. S.—A complicating feature in the behavior of the human anti-Rh sera is their failure to give entirely parallel reactions when tested with numerous bloods.[14, 17] Thus these sera give varying incidences of Rh– reactions (Table II).

TABLE II. RESULTS OF PARALLEL TESTS ON 334 RANDOM BLOODS OF ALL GROUPS

ANTI-Rh SERUM FROM PATIENT	PER CENT	
	Rh+	Rh–
E. B.	87	13
M. F.	85	15
M. S.	73	27

The greater incidence of Rh– reactions with serum M. S. is manifested by the fact that some bloods diagnosed as Rh+ in their reactions with sera E. B. or M. F. are not agglutinated by serum M. S.* This fact is applicable to the bloods of only 3 of the 29 mothers which were tested with each of the three sera.

These serologic observations which are of more than academic interest, will be published in detail elsewhere, but reference will be made later (page 932) to the significance of these findings in connection with the iso-immunization by the fetus.

Statistical Data on the Rh Blood Factor in 153 Mothers of Infants with Erythroblastosis Fetalis.—This study reveals an incidence of about 90 per cent Rh– reactions in contrast to 15 per cent Rh– reactions in the random population. The actual analysis is rendered somewhat complex because not all bloods were tested with each of the three anti-Rh sera (Table III).

TABLE III

ANTI-Rh SERUM	NUMBER OF MOTHERS' BLOODS TESTED	PER CENT	
		Rh+	Rh–
M. F.	142	10	90
E. B.	60	15	85
M. S.	28	7	93
Combined results	153	7	93

The higher incidence of Rh+ with serum E. B. is due to the fact that more mothers Rh+ with serum M. F. were tested with serum E. B. than with serum M. S. At least one of the bloods Rh+ with serum E. B. can be considered Rh–, because this blood contains very active anti-Rh agglutinins.

*Very rarely, the converse specific effect is obtained, i.e., blood Rh- with serum M. F. is Rh+ with serum E. B. or M. S.

Three mothers whose blood was Rh+ with serum M. F. or E. B. were Rh– with serum M. S. These three cases listed as Rh– could be considered as instances in which iso-immunization could occur, because in two instances the husband's blood, and in the third the affected child's blood were Rh+ with each of the three sera.

The striking difference in the incidence of the Rh factor in the selected population of mothers with erythroblastic babies and in the random population strongly supports the concept of iso-immunization. Since the incidence of Rh– bloods is very high in these mothers, it could be anticipated on the basis of the iso-immunization theory that the affected infants and the fathers in the series of Rh– mothers are exclusively Rh+. As will be shown such results were obtained in tests on 89 fathers and on 76 infants in whom a diagnosis of erythroblastosis fetalis was made (Table IV).

TABLE IV. INCIDENCE OF RH+ AND RH– IN HUSBANDS AND AFFECTED INFANTS OF THE 141 RH– MOTHERS

	NUMBER TESTED	Rh+	Rh–	EXPECTANCY OF Rh– IN RANDOM POPULATION
Husbands	89	89	0	13 (89 × 15%)
Affected infants	76	76	0	11 (76 × 15%)

The findings in this table are based on tests with serum M. F. which gives an incidence of 15% Rh– reactions.

The findings in Tables III and IV strongly indicate the iso-immunization of the Rh– mother by the Rh factor in fetal blood. The final proof for such iso-immunization can be supplied only by the demonstration of anti-Rh agglutinins in the mother's blood. Obviously, the likelihood of finding such agglutinins will be greater if the mother's blood is tested soon after the delivery of an infant suffering from erythroblastosis fetalis. This is borne out by the findings presented in Table V.

TABLE V. INCIDENCE OF ANTI-RH AGGLUTININS IN 141 RH– MOTHERS

INTERVAL AFTER LAST DELIVERY OF AN AFFECTED INFANT	AGGLUTININS PRESENT	AGGLUTININS NOT FOUND
2 months post partum	33	37
2 months to 1 year past partum	5	15
1 year or longer post partum	2	39
During next pregnancy	2	5
No data	0	3
Total	42	99

The failure to detect anti-Rh agglutinins in many cases tested shortly after the delivery of an affected infant does not exclude their presence at some previous period during the course of their pregnancy. Since the course of antibody production in general is characterized by a gradual rise, a period of maximum activity, and gradual disappearance, it is conceivable that in some cases anti-Rh agglutinins, after exerting their lytic effect on the fetus, rapidly disappeared from the blood so that none could be demonstrated at the time of delivery. It is therefore indicated that the bloods of mothers known to have delivered babies with erythroblastosis fetalis be studied at several intervals during course of future pregnancies. Furthermore, it is conceivable that antibodies capable of reacting in vivo cannot be demonstrated because of limitations in the sensitivity of the technique employed.

It is of great interest that the anti-Rh agglutinins may be demonstrable for such unusually long periods, as two years post partum. Probably the long duration indicates an intense degree of iso-immunization which may perhaps influence the outcome of the next pregnancy with an Rh+ fetus. More specifically, reference is made to the clinical observation on the high incidence of spontaneous abortions and miscarriages in mothers of infants with erythroblastosis fetalis (p. 933).[3, 18, 19]

The results shown in Tables III, IV, and V indicate that a combination of Rh– mother, Rh+ father, and affected infant can be used as a laboratory test to support a diagnosis of erythroblastosis fetalis. Such results which are present in about 90 per cent of the cases should be of value in the diagnosis of mild, atypical, or borderline cases of this condition.

The 11 Cases in Which Iso-immunization with Rh is Excluded.—When these exceptional cases were first observed, it was assumed that blood factors other than Rh may also induce iso-immunization. This explanation seemed plausible since Levine and Polayes[20] had already demonstrated a new blood factor by means of an atypical hemolysin found to be the cause of a post-partum transfusion reaction.* Indeed, this antibody seemed to differentiate the bloods of several of the Rh+ mothers from those of their husbands or affected children in a manner compatible with the concept of iso-immunization. However, the results were only suggestive and further study was hampered by the weak activity of the antibody.

More decisive results, however, were obtained with the reactions of an atypical agglutinin found in the serum of one of the 11 Rh+ mothers (patient K. F.).[21] This patient of Dr. Javert had one full-term, normal pregnancy; one infant with erythroblastosis fetalis (1937) and a missed abortion. When tested she was again several months pregnant. The antibody in this serum gives strong reactions almost exclusively on bloods which are Rh– with serum M. S. Accordingly, the blood factor identified by this atypical agglutinin must have some genetic relationship with Rh. Since this serum became available late in the course of this study, the bloods of the remaining mothers of this group must be retested with this new agglutinin.

Reference again is made (p. 931) to the bloods of 3 mothers of erythroblastic babies which were Rh+ with two anti-Rh sera but Rh– with the third serum M. S. These cases were included in the Rh– series because in one instance the husband and in the other the affected child were Rh+ with each of the three anti-Rh sera.

The Theory of Heterospecific Pregnancy.—The Distribution of Blood Factors A, B, and Rh in Red Blood Cells, Tissue Cells, and Body Fluids.—It is of interest that a difference in the blood groups of mother and infant was the basis of an older theory on the pathogenesis of familial icterus gravis.†[22, 23] In the literature, this concept has been referred to as "heterospecific pregnancy." The theory, since abandoned

*This mother had 4 miscarriages and 8 full-term, presumably normal infants.

†At that time (1923) the more comprehensive term, erythroblastosis fetalis, was not yet in use.

for lack of evidence, does not differ in principle from the iso-immunization theory in which the Rh factor plays such a prominent role. According to the concept of heterospecific pregnancy, given a mother of Group O and an infant of Group A (or Group B), the maternal anti-A (or anti-B) agglutinins are theoretically capable of acting on the Group A (or Group B) fetal blood. Actually, there is now evidence that in the example cited the mother's normal iso-agglutinin anti-A (or anti-B) is increased in titer as a result of iso-immunization with the A (or B) blood of the fetus.[24, 25] Nevertheless, the maternal agglutinins are specifically inhibited from acting on the fetal blood because of the wide distribution of the A and B factors in tissues and body fluids.

However, this applies to about 80 per cent of all individuals (secretors)[26] and if a fetus of Group A belongs to the class of nonsecretors (20 per cent), it is conceivable that the maternal iso-agglutinin anti-A may serve as the source of the intrauterine hemolytic process. Accordingly, the older theory of heterospecific pregnancy may have to be invoked at least for selected cases of erythroblastosis fetalis in which the Rh or other blood factors fail to indicate iso-immunization by the fetus.

From these considerations on heterospecific pregnancy and in view of the established importance of the Rh factor in the pathogenesis of erythroblastosis fetalis, it can be assumed that the Rh factor is probably not present in tissue cells or body fluids, but rather is limited to red blood cells only. Otherwise, the maternal anti-Rh agglutinins would be specifically inactivated and therefore incapable of inducing the hemolytic action on the Rh+ fetal blood. Tests made by Levine and Katzin[27] with numerous specimens of saliva, a few specimens of sperm cells, and seminal fluid, indicate that the Rh factor is not present in the material tested.*

Iso-immunization in Habitual Abortion and Stillbirth.—Reports from the literature indicate that the obstetric history of mothers of infants with erythroblastosis fetalis reveals a high incidence of abortions, miscarriages, and stillbirths. Macklin[18] and Darrow[19] stated that the mechanism responsible for the pathogenesis of erythroblastosis fetalis applies also for these abortions and stillbirths. This view is supported by the results in the present study. That iso-immunization by the fetus and subsequent action of maternal agglutinins on fetal blood may be the mechanism of these abortions and stillbirths is indicated in the data presented in Table I.[3, 4]

Another group of women were investigated because of their history of habitual abortion and stillbirths, but these women had no infants with erythroblastosis fetalis. Many of these women were Rh– but a satisfactory statistical analysis similar to the study on erythroblastosis fetalis is more difficult because habitual abortions and stillbirths may be manifestations of many conditions. Nevertheless, there is sufficient evidence in at least five† cases of this group to include them with the mothers of erythroblastic infants, because iso-immunization by the Rh factor in the fetus could be demonstrated. In each of these cases, anti-Rh ag-

*Similar observations on saliva were recently reported by Wiener and Forer.[28]

†Four of these patients were discussed in our previous papers.[1-3]

glutinins were observed. Three of these patients suffered from intragroup transfusion accidents following an abortion or stillbirths.

Two of these 5 patients had just delivered presumably normal infants in spite of the presence of moderately active anti-Rh agglutinins. Unfortunately, hematologic and other clinical data were not obtained so that a mild form of erythroblastosis fetalis could not be entirely excluded. However, the obstetric histories reveal that one of these patients (H. H.) had three consecutive miscarriages and the other (L. L.) had two miscarriages and one premature infant who survived for ten days.

The association of intragroup transfusion accidents, in the presence of atypical agglutinins, in three patients following an abortion, a miscarriage, and a stillbirth, respectively, was observed by us in the analysis of reports by Parr and Krischner,[29] Johnson,[30] and Zacho.[31] Other instances of intragroup transfusion accidents following abortions, miscarriages, or stillbirths, in the absence of atypical agglutinins have been reported by several authors.[32, 33] Very probably the transfusion accidents reported in the five papers quoted are ultimately attributable to iso-immunization by the fetus.

In any event, it is the action of maternal immune agglutinins on the fetus which may cause its death at any stage of its development so that the same mechanism may be responsible for erythroblastosis fetalis in the surviving infant as well as some cases of habitual abortion.

DISCUSSION

The numerous theories on the pathogenesis of erythroblastosis fetalis were recently reviewed by Darrow[19] who, in a hypothetical discussion, anticipated the iso-immunization theory. This author suggested an antigen-antibody reaction based on differences in maternal and fetal hemoglobin or other constituents of red blood cells as the most plausible explanation. A similar view was previously mentioned by Ottenberg,[23] but neither author presented experimental data to support their theses.

The findings presented establish the significant role of iso-immunization of the mother by blood factors in the fetus in the pathogenesis of erythroblastosis fetalis. Of prime importance is the Rh factor in the fetal blood which is transmitted as a dominant mendelian gene from the father.[14] Statistical evidence was offered to prove that its presence in the blood of the father and affected infant is a prerequisite condition for the iso-immunization of the Rh– mother. But in the final analysis, the proof of iso-immunization by the Rh factor was the demonstration in many instances of anti-Rh agglutinins in the mother's blood. It is the continuous intrauterine action of anti-Rh agglutinins with the Rh positive fetal blood over a period varying from weeks to months which causes a progressive hemolysis of fetal blood.

The reaction of anti-Rh antibody and Rh blood takes the form of agglutination in the test tube but in the fetal circulation the end result is hemolysis. Attempts to demonstrate corresponding hemolytic reaction in the test tube by the addition of fresh human serum have so far failed.

One of the most striking features of erythroblastosis fetalis is the wide variety of clinical syndromes it embraces, such as, the extremely fatal form of fetal hydrops and the mild, frequently unrecognizable anemias of the newborn.[34] These clinical forms are probably the result of varying degrees and duration of iso-immunization during the course of the pregnancy. Nothing is as yet known concerning the exact time and conditions during the course of the pregnancy when iso-immunization begins. If some cases of habitual abortions are a manifestation of iso-immunization, then the process may start shortly after conception occurs. At any rate, it is conceivable that the prolonged action of immune iso-agglutinins on the susceptible fetal blood may induce more severe damage than the action of agglutinins produced very late in the course of a pregnancy.

The clinical observation has been made that some infants may be born apparently free from the condition, but in the course of a few days, severe anemia and jaundice make their appearance. It is difficult to correlate this fact with the iso-immunization theory since the infant after birth should be free from any further action by the maternal agglutinins. The source of the delayed hemolysis has been suspected to be the colostrum, but in a number of these cases the infant was not breast fed. An alternative explanation is the storage of mother's agglutinins by the tissue of the fetus so that their subsequent release may then induce the hemolysis several days after birth.

A few practical applications based on these studies are of importance to the obstetrician. In the first place the data presented make it clear why caution must be exercised in selecting compatible donors for transfusing mothers of infants with erythroblastosis fetalis or those with a history of habitual abortions, a stillbirth, or a neonatal death. It is of interest that 8 of the 141 Rh– mothers suffered from severe intragroup transfusion reactions. Such accidents can be prevented if Rh– donors are available for Rh– mothers[3] and if the modified compatibility (cross-matching) test be employed for the detection of the "warm" anti-Rh agglutinins (p. 927).[4, 11, 12]

Furthermore, there are indications from a small number of cases that the affected infant maintains higher levels of hemoglobin and red blood cell counts if he is transfused with Rh– blood instead of Rh+ blood. The rationale for this suggestion is drawn from the fact that the infant's own Rh+ blood is undergoing destruction.[35]

The hereditary nature of erythroblastosis fetalis, hitherto unknown, can now be stated in terms of the iso-immunization theory. In some families, every pregnancy but perhaps the first, terminates in either an abortion, a stillbirth, or an infant with erythroblastosis fetalis; while in other families, only one of several pregnancies results in an affected infant. Since the Rh factor is inherited as a simple mendelian dominant,[14] it is obvious from a genetic standpoint, that this striking difference in familial incidence of the disease is determined by the homozygosity (RhRh) or heterozygosity (Rhrh) of the father's blood.[36] The genetic details and evidence supporting this concept will be given elsewhere. It is, however, appropriate to state at this point, that the first born is frequently but not always spared because more than one preg-

nancy with an Rh+ fetus may be required before a sufficient degree of iso-immunization is attained.

It has been recorded by Javert[37] that erythroblastosis fetalis in one of its several forms, occurs once in 400 deliveries, but it is probable that this condition has a still higher frequency, especially if some cases of habitual abortion and stillbirths are manifestations of iso-immunization. Actually, the incidence of matings in which iso-immunization with Rh may occur (Rh+ husband and Rh– wife) is 85 by 15 or 13 per cent of all matings. Consequently, one would expect a much higher incidence of erythroblastosis fetalis. There are, however, a number of factors tending to reduce this incidence, such as, for example, the current tendency to small families and the inability of many Rh– women to respond to iso-immunization.

The data on erythroblastosis fetalis and the recent studies on the iso-immunization with the blood factors A and B in the absence of any pathologic conditions in the mother or the infant indicates that immunizing substances derived from the fetus make their way through the placental barrier into the maternal circulation. Since the Rh factor, in contrast to the A and B substances, is probably limited to only red blood cells, it is assumed that fetal blood in one form or another penetrates the villus in sufficient quantity to induce immunization in the mother.

SUMMARY AND CONCLUSIONS

1. In 93 per cent of the cases investigated, erythroblastosis fetalis results from the iso-immunization of the Rh– mother by the Rh factor in the red blood cells of the fetus.

2. In the remaining cases, blood factors other than Rh are responsible for the iso-immunization.

3. Agglutination tests for the Rh factor are of value as a laboratory aid in the diagnosis of erythroblastosis fetalis.

4. The pathologic manifestations of this disease are produced by the intrauterine action of maternal immune agglutinins on the susceptible red blood cells of the fetus.

5. It is probable that iso-immunization is also the cause of a certain proportion of habitual abortions and stillbirths.

6. Intra-group transfusion accidents associated with pregnancy can now be prevented by the use of Rh– donors and by means of modified cross-matching test.

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THE OCCIPITOPOSTERIOR POSITION*

ITS MECHANISM AND TREATMENT

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THE problems presented by the occipitoposterior position have been the subject of many studies and much controversy. My only apology for reconsidering this subject arises from the fact that at the Sloane Hospital for Women we have been studying the pelvis and the correlated mechanisms of labor with the aid of the x-ray in a large number of cases of all types. Among these a random selection of 100 occipitoposteriors that terminated in easy spontaneous or low forceps deliveries and an equal number of midpelvic arrests provided two contrasting groups for study. The data obtained in the course of a careful study of these cases is the basis for the present report.

ETIOLOGY

A close relationship of the shape of the pelvic brim to the engaging position of the vertex has been shown previously by Thoms and in several communications from the Sloane Hospital. It has been stated that the anthropoid pelvis favors the posterior position. One of the most striking observations in this series was the high incidence (83 per cent) of some degree of narrowing of the fore pelvis in pelves associated with a primary occipitoposterior position. In addition to the narrowing of the fore pelvis, it was noted that the pelvis almost

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invariably showed a true conjugate of average length. It seems reasonable, therefore, to postulate that the occipitoposterior position is caused, in the main, by adaptation of the head to an inlet possessing a narrow fore pelvis and an ample anteroposterior diameter. In this way, the larger occipital part of the fetal head avoids the narrowest segment of the pelvic brim. The pelvic type which comes nearest to these specifications is the anthropoid variety, and consequently it is found that these forms largely account for most of the primary posteriors. However, a gynecoid type with a narrow fore pelvis or an android-anthropoid type may favor this position, for both satisfy the pelvic architectural requirements mentioned.

An attempt was made to ascertain, if possible, why a primary occipitoposterior position occurred in the remaining 17 per cent (34 cases) that did not show a narrowing of the fore pelvis. Of these, it may be said that in 10 cases the pelvis was so large or the baby so small in relation to the pelvis that the factors which ordinarily make it necessary for adjustment of the head to the optimum inlet diameters did not come into play, and the occipitoposterior position could be largely ascribed to a matter of chance. The same may be said of an additional 4 cases in which the inlet was so symmetrically round that no particular position was favored and chance may have played a similar role. At least 90 per cent of the primary posterior positions, therefore, may be accounted for on the basis of the variations in the pelvic architecture at the pelvic inlet.

The secondary occipitoposterior positions, that is, those cases which engaged in some position other than the occipitoposterior and rotated to the posterior lower in the pelvis, represent variations of the internal rotation mechanism and will be considered later under that heading.

Another point that should be mentioned here deals with variations in degrees of occipitoposterior positions. Ordinarily when we speak of the vertex in the R.O.P. position we infer that the sagittal suture occupies the right oblique diameter of the inlet. This is not entirely true in all cases. Actually it is noted that the sagittal suture may occupy a number of intervening oblique axes so that some posterior positions engage with the occiput just slightly posterior to true transverse while others engage in the generally accepted oblique diameter of the brim and still others engage almost directly posterior. The pelvis plays an all important role in determining the degree to which the occiput is posterior for, it is noted, that the more narrow the brim the more posterior is the occiput. The practical significance of these variations in the degree to which the occiput is posterior is related to the mechanism of descent, because in the true primary posteriors, as we may designate those posteriors in which the occiput is at or behind the sacroiliac synchondrosis, the fetal back practically overlies the mother's spine and, as will be shown later, the axis of fetal drive is not as favorable as when the occiput and back are more anterior.

If it is true then that the occipitoposterior position represents correct adaptation of the fetal head to the shape of the brim, we should not consider it a malposition but rather as the optimum position for

the pelvis in which it occurs. In fact it could be argued that many occipitoposterior positions would meet with serious obstruction if they were forced to engage in any other position. For this reason there seems to be no justification for the prophylactic use of pads as advocated by Buist to correct an occipitoposterior position. Only when the posterior occurs in one of the well-formed round-inlet types in which an anterior position is theoretically just as favorable as the posterior does such a procedure seem at all justifiable. The physiologic normality of the occipitoposterior, however, does not remove the condition from the dystocia problem as the data obtained from our clinic show. We note that while 19 per cent of all vertex presentations engage in the posterior position, 44 per cent of the midforceps deliveries are associated with this position (Table I).

TABLE I. MIDFORCEPS IN RELATION TO POSITION OF ENGAGEMENT

6440 Deliveries—283 Midforceps

INCIDENCE OF POSITION OF ENGAGEMENT IN 6440 CONSECUTIVE DELIVERIES		INCIDENCE OF POSITION OF ENGAGEMENT IN 283 MIDFORCEPS DELIVERIES	
O.T.	60.4%	O.T.	41.6%
O.P.	19.2%	O.P.	44.2%
O.A.	20.4%	O.A.	14.2%

Actually this concept of the etiology of the posterior position simply removes the emphasis from the position itself one stage back to the pelvis that caused it. This is shown clearly in Table II which is a comparison between the occipitoposterior positions that gave no particular difficulty and those that resulted in varying degrees of midpelvic arrests.

TABLE II. OCCIPITOPOSTERIOR POSITIONS. COMPARISON OF PELVES AND BABIES IN 100 SPONTANEOUS AND 100 MIDFORCEPS DELIVERIES

	FETUS 8 LB.	MALE CHARACTER BRIM	BRIM UNDER AVERAGE	SACRUM FORWARD	CONVERGING SIDE WALLS	ARCH UNDER AVERAGE
Spontaneous	26%	23%	13%	15%	25%	23%
Midforceps	41%	31%	47%	34%	56%	36%

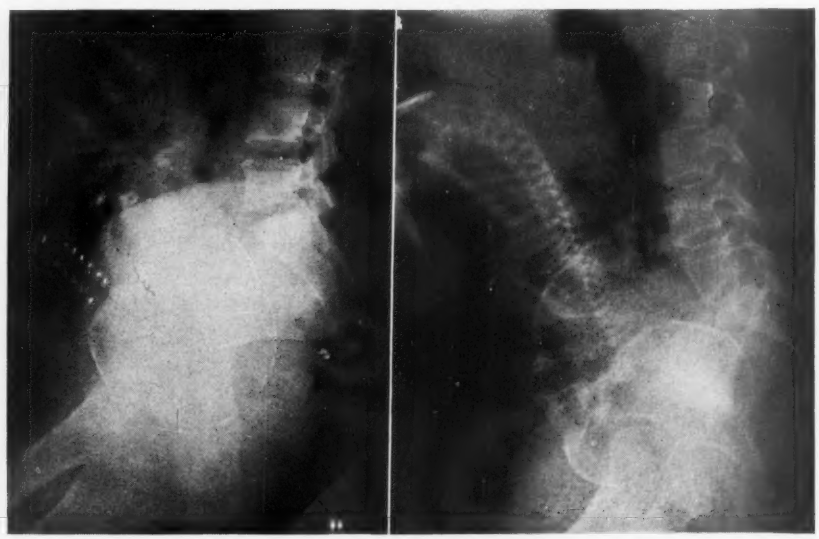
This leads us to conclude that large babies, small inlets, male characters, as well as the forward sacrum, convergence of the side walls, and narrow arches are distinct factors in the group which gave difficulty. The importance of the pelvis as a factor in the difficult labors associated with the occipitoposterior position has not received the attention which it deserves. Except for reports by Plass, Cosgrove, and Harper very little in the way of serious consideration has been given to this phase of the problem. A careful study of the pelvis in its entirety therefore will yield most valuable information upon which to base a prognosis of labor in these cases.

However interesting this comparison between the spontaneous and midforceps occipitoposterior deliveries may be, it should be borne in mind that a similar comparison in the other vertex positions would also bring out striking differences in the pelves of the spontaneous

cases when contrasted to those which resulted in dystocia. The evidence brought out so far, therefore, does not completely explain why the occipitoposterior position in contrast to the other vertex positions is associated with a higher incidence of difficulty in labor. To find the answer to this question we must turn to the details of the mechanism of the occipitoposterior position.

DESCENT, FLEXION, AND EXTENSION IN THE OCCIPITOPOSTERIOR POSITIONS

In Fig. 1 are contrasted the lateral views of an occipitoanterior and a true occipitoposterior position. These views include sufficient area to show the maternal pelvis and spine as well as the fetal spine and cranial ovoid. The x-rays were taken under similar conditions with the patient recumbent on her side between contractions. Two very characteristic differences stand out (Fig. 2). First, it is noted that a



A. *B.*

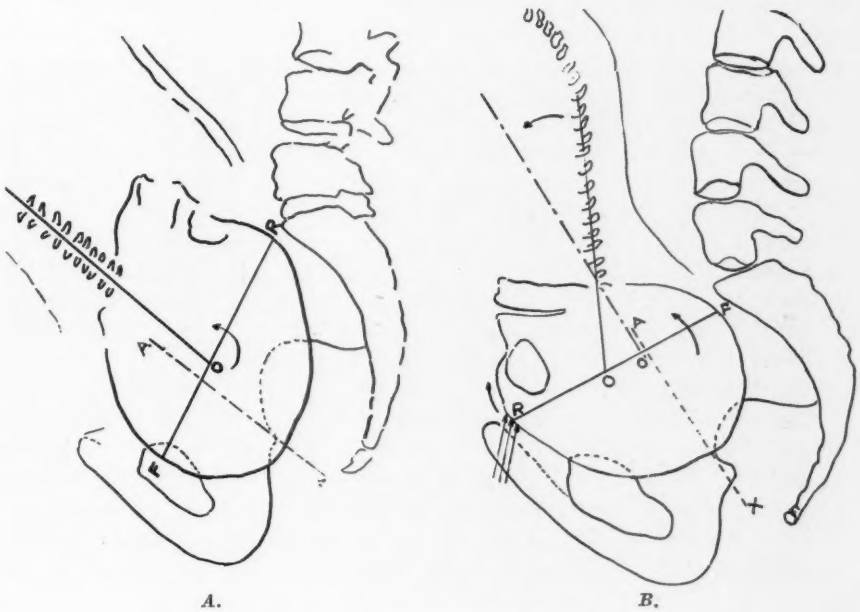
Fig. 1.—*A*, Lateral view, occipitoanterior position. *B*, Lateral view, occipitoposterior position.

line drawn through the fetal spine, while practically continuous as a straight line with the pelvic axis (AX) in the anterior case, is definitely at an angle with the pelvic axis in the posterior. Another difference is also obvious. In the anterior position, the cranial ovoid in a state of flexion presents its long axis more or less in the axis of the pelvis while in the posterior the length of the ovoid in extension runs more nearly across the pelvic axis. Repeated observations of similar lateral films have brought out the consistency of these fetal-maternal relationships in the true occipitoposterior positions.

While extension in the posterior position has been reported by practically every writer on the subject and seems to be a well-established aspect of the posterior mechanism, its cause has not been well understood. An explanation of this mechanism must begin with the assump-

tion that there is a downward force transmitted to the fetal head along the rigid fetal spine. This has been shown by Lahs, Olshausen, Warnekros, and others. They have stated that even when the membranes are not ruptured the effective force of uterine contraction and retraction is exerted largely by pressure of the fundus on the upper fetal pole and that this is transmitted directly to the presenting part by the vertebral column.

Some of the newer views concerning the behavior of the uterus during labor do not detract from the validity of this statement, for irrespective of the behavior of the uterine muscle there must be a resultant downward force which has the effect of changing the level of the fetus in the axis of the pelvis, and this force must be transmitted to the fetal



A. *B.*

Fig. 2.—Direct tracing of Fig. 1.

head along the rigid fetal spine. This view is further supported by the frequent x-ray observation of the fact that with active labor the fetal spine becomes changed from a structure having a well-defined rounded curve to one which is straight and apparently rigid. This rigidity of the spine is maintained both during and between contractions. Now if this force is applied to the head at the foramen magnum it will result in both descent of the head and a torque motion around the atlas. This torque motion will produce either flexion or extension, depending upon the lengths of the two lever arms formed. A common explanation for the cause of flexion is that it results from the fact that the distance from the foramen magnum to the chin is longer than from the foramen magnum to the occipital protuberance, and that in accordance with the law of the lever the long arm will ascend when resistance is met by the head.

Since these anatomic points are fixed, it would seem impossible for extension ever to occur, for the lever arms cannot vary under these circumstances. This explanation of flexion, therefore, cannot be correct, since it does not permit an explanation of extension, which is an observed mechanism. In another and more reasonable explanation of flexion, the lengths of the lever arms are determined by projecting the line of force through the fetal spine and foramen magnum to the occipitofrontal plane. This is more nearly correct, since it permits of varying lengths of the lever arms depending upon the angle at which the force transmitted through the fetal spine is directed to the occipitofrontal plane. However, it is apparent that flexion and extension may take place even before the occipitofrontal plane becomes functional in the mechanism of descent. Actually it is upon the cranial plane of greatest friction that the forces which produce extension and flexion become operative and for this reason the mechanism is best explained by stating that flexion will result when the line of force through the fetal spine intersects the long axis of the cranial plane of greatest friction in such a manner that the frontal lever arm thus formed is longer than the occipital. Conversely, extension will result when the occipital lever arm is longer than the frontal. In Fig. 2 the cranial planes of greatest friction are planes *FR* and the line of force through the fetal spine meets this plane at *O*. It will be seen that the long arms are different in the two cases. In the anterior the long arm extends to the frontal region and is effective in producing further flexion, while in the posterior the long arm extends to the occipital region and results in extension.

From the foregoing it becomes obvious that the fetal axis along which the resultant expulsive force of the uterus is exerted is important first, because it may result in either an efficient straight line drive in the axis of the pelvis or one which is at an angle to the axis of descent with a partial loss of effective expulsive force, and second, because of the varying degrees of flexion or extension which it may bring about. To introduce a practical point, suppose the fetal axis in Fig. 2, *B* were to make a forward excursion as indicated. Now the lever arms become changed in their lengths and a flexion force is introduced. From these theoretical considerations, therefore, it should be desirable to maintain the fetal axis of the posterior position as far forward as possible. This can be helped by having the patient in labor maintain the upright position as long as it is possible for her to do so, since this favors a forward excursion of the back. While the upright position is the most favorable, it would seem that the supine position is the most disadvantageous for the occipitoposterior mechanism. When the patient finally must take to her bed, it would seem desirable that she should lie on her side in order to permit the forward excursion of the uterus during a contraction to be utilized to the fullest extent. It also seems obvious that binders are contraindicated. What is desired is the very opposite of what the binder achieves.

One of the factors responsible for the greater ease with which the multipara delivers the child in the occipitoposterior position may be the

forward excursion of the uterus and the fetal back resulting from the greater relaxation of the abdominal walls. This should favor flexion and a better axis of drive. This same forward excursion of the fetus may take place when the membranes rupture. The marked improvement in the efficiency of labor which followed the rupture of the membranes in several of our cases may have been due to this cause. Theoretically then, rupture of the membranes may favorably alter the pattern of labor by causing the fetal back to go forward. It will be of interest to study this in detail later on.

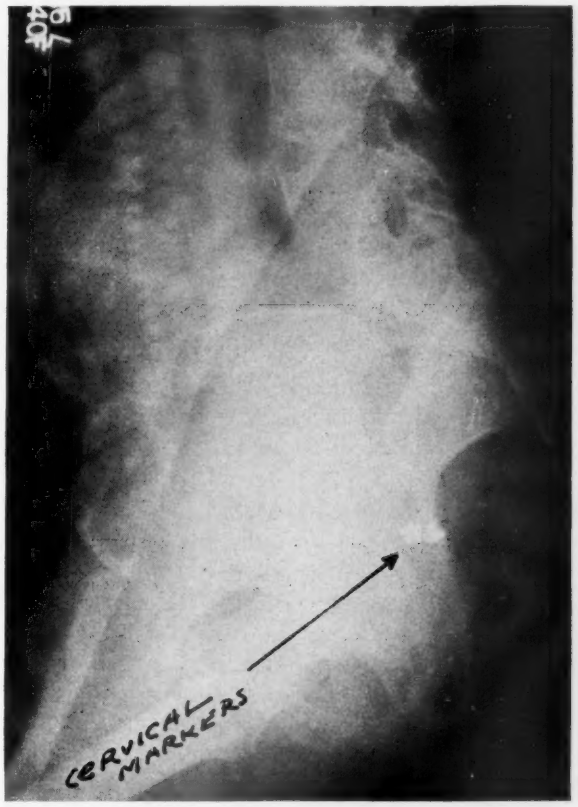


Fig. 3.—Lead shot markers sutured to anterior and posterior cervical lips, R.O.P. position. Cervix 2 cm. dilated.

A point about extension which is clinically important is the fact that when the head is in extension the frontal region frequently bulges above the symphysis and gives the impression of disproportion. It has been found repeatedly that in many such cases when the patient assumes the upright position for the lateral x-ray film, the level of the head changes remarkably and frequently appears well engaged. Much profitable information can be obtained by suprapubic palpation in the upright position when the head is unengaged.

One of the difficult problems in the occipitoposterior position is the behavior of the cervix. It is well known that the cervix is slow in

dilating and frequently fails to dilate completely even after a long labor. It would be beyond the scope of this paper to make any attempt to go into the causes of so-called cervical dystocia, but one fact becomes apparent when we study the lateral x-rays of the posterior positions and compare them with the anterior positions. If we consider the cranial ovoid as egg-shaped, it is noted that the point of the ovoid or its long axis is invariably pointed down when the position is anterior, while the long axis extends more nearly across the pelvis in the posterior positions. In Fig. 3 the cervix is located with lead-shot markers on each lip. The cervical canal must dilate and the lips retract over the head. The area over which this retraction has to take place is much greater in posterior positions of the head. This accounts for the frequently noted findings of a cervix, which although reasonably well dilated, seems to be far from the periphery of the head and remains as a definite and formidable rim all around. In addition to this it is possible that less efficiency in the dilating mechanism results from the fact that the cervix has to be retracted along a wide flat surface of the fetal head almost at right angles to the uterine axis in contrast to the more nearly vertical retraction over the long vertical oval of the well-flexed head.

FLEXION

From what has already been said, it becomes obvious that the lack of flexion is an important factor in the mechanism of the occipitoposterior position. The child's head eventually becomes flexed but this occurs only after a forward excursion of the fetal axis takes place. If we conceive of the previously discussed extension force acting unchecked, then, theoretically, the head should continue to extend until an equilibrium is reached when it cannot extend further. This would not occur until a full face presentation obtained. Long before this degree of extension takes place, however, the frontal region meets with resistance in the fore pelvis (arrows Fig. 2, *B*). Resistance at this point will completely check any further extension, since the fore pelvis acts as an unyielding block below the frontal bone. Let us assume further that the direction of force exerted through the fetal spine remains unchanged so that the lever action is still one of extension. It now becomes obvious that since further extension is blocked by the fore pelvis the only positive result of the uterine contractions is a backward and downward slide of the fetal head, resulting from the fraction of the force which is not dissipated in the blocked-up extension component. The counter force exerted by the fore pelvis against the frontal region of the head is not entirely passive, for we frequently note that it results in a good deal of molding by pushing the frontal bones under the parietals at the very point where the pressure is exerted (see Fig. 13). This same force acting over a long period of time may eventually pinch off the stretched cervix, resulting in passive congestion and edema of the anterior lip.

Depending upon the amount of available space in the upper pelvis, the head moves down in the extended position, sometimes quickly,

more often slowly, and occasionally not at all under the impulse of only a fraction of the uterine force. Now as the head slowly descends downward and backward, the fetal back, being limited by the posterior uterine wall, must accommodate itself to the lower position of the fetal head by moving forward. This changes the lengths of the lever arms as previously illustrated and a flexion force is introduced. While this forward excursion of the fetal back may take place solely from the increased rise of the uterus as the contractions become stronger, it usually does not occur until a sufficient amount of descent has taken place to force the fetal back forward. As a consequence it is noted that complete flexion does not usually take place until the head is well down in the pelvis. This mechanism of flexion goes on slowly as the fetal axis moves forward in response to the descent of the head. Flexion, therefore, is ultimately dependent upon descent of the fetal head. When the upper pelvis is abnormal in either shape or size, it interferes with descent and this in turn prevents proper flexion thereby multiplying the difficulties. When the pelvis is ample, even the partially extended head will descend without much difficulty, become flexed, and there is a comparatively easy labor. An abnormal pelvis and a posterior position may therefore react upon each other to produce a really difficult labor.

As will be shown later, many of the so-called midpelvic arrests occur because of factors existing at the brim. When preparing to do a midforceps operation with the head in the posterior position and definitely extended, the conditions prevailing at the brim should always be considered, even though the lowest part of the molded head seems to be fairly well down in midpelvis.

Since flexion is so important, we naturally want to know how it may be brought about. Posture of the patient has already been considered. Pressure against the frontal bone carried out with each pain under nitrous oxide anesthesia should be helpful if the procedure is carried out over a sufficiently long time. Manual stretching of the cervix may be combined with this when dilatation has come to a standstill. In this way, by removing the resistance of the soft tissues, the full effect of that fraction of the uterine force which is not dissipated in extension is applied to bringing the head lower in the pelvis, which in turn will bring the back forward. Since this will result in greater flexion and smaller presenting diameters, it will be followed by more descent and so a favorable chain of events may be initiated.

Flexion will also follow a change of the fetal axis by turning the child completely, both head and shoulders, to an anterior position following which the patient is allowed to have further labor. Douglas Miller has advocated this method, and although we have no experience with it, there is reason to endorse its mechanical soundness. However, it should be stated that such a procedure would be feasible only when labor has progressed sufficiently to allow molding of the fetal head, otherwise the unmolded head would meet the very resistance in the fore pelvis which caused the posterior position to occur in the first place.

ROTATION

When the matter of internal rotation as related to the occipitoposterior positions was considered, it seemed necessary to reinvestigate its causes, since it seemed obvious that the present concepts of this important mechanism did not account for the observed facts. It soon became apparent that this was the real nucleus of the investigation for the reason that practically all the arrests occurred with the head unrotated and that therefore a good deal of the dystocia could be related to a failure of this mechanism. Also from a practical point of view it

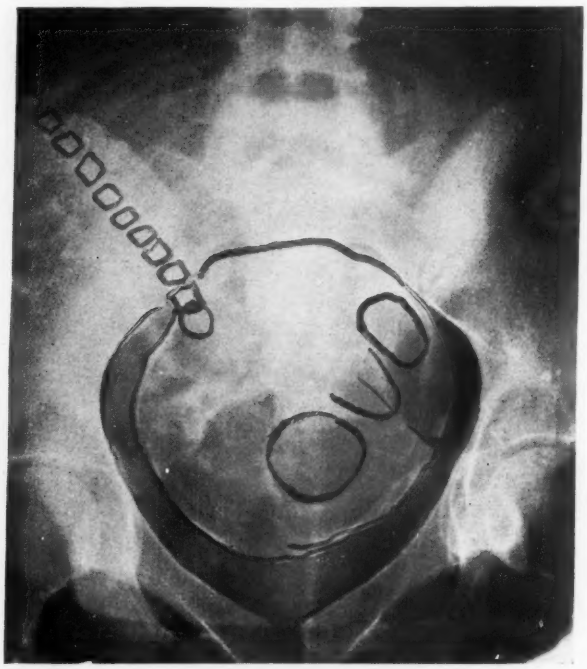


Fig. 4.—Head in R.O.A. position at onset of labor became adjusted to R.O.P. position as labor advanced.

seemed obvious that a complete understanding of the details of rotation would be important, since we are frequently called upon to reduplicate this mechanism in the course of an operative delivery, and unless we fully understand its underlying cause and the reasons for its failure, we are not equipped to carry out many of the more difficult obstetric operations.

The theory of internal rotation which at the present time is most generally accepted was first considered by West in 1856. He stated that the head was rotated by the inclined planes of the pelvic floor and that whatever part of the child reached the pelvic floor first was rotated to the front. On the basis of this theory the head will always turn to the front except in those posterior positions with deflexion, in which case the sinciput will rotate to the front while the occiput rotates posteriorly. There has been little objection to this concept of rotation,

because it seems to explain satisfactorily for the first time the mechanism of short rotation to the hollow of the sacrum. In the light of our present investigation, however, there are some objections to this theory, for it seems that many posterior and transverse presentations that are not extended rotate backwards. In other words, the direction of rotation does not depend directly upon flexion or extension.

In fact a searching study of all the theories on the cause of internal rotation leaves one with the thought that there is no single theory that explains all the phases of this mechanism satisfactorily. With this in mind an attempt was made to see if the material in this study could provide a more complete explanation of this important mechanism. Before presenting these views on the subject, it might be well to call attention to a simple form of rotation which has been frequently noted to occur at the brim before engagement (Fig. 4). The case shown in Fig. 4 started labor with the head dipping into the brim in the R.O.A.

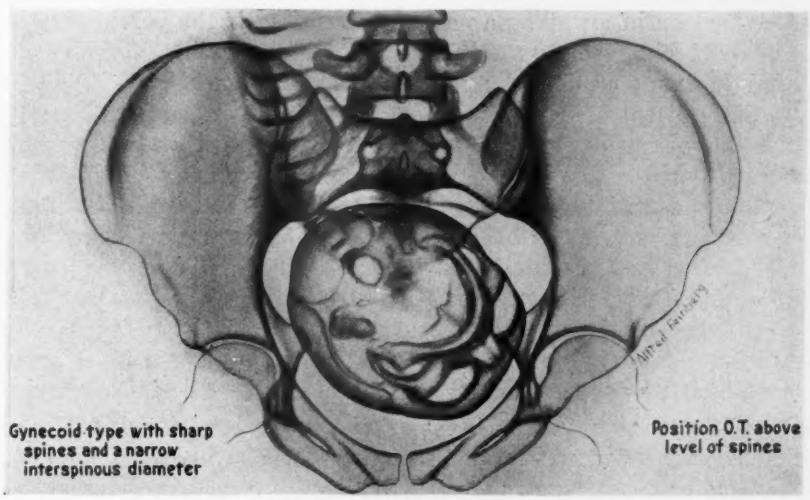


Fig. 5.—Secondary oblique occipitoposterior position. Occiput rotated from an R.O.T. to an R.O.P. position moving away from the resistance of the spines in front into ample posterior sagittal diameters at the interspinous level.

position, but under the influence of labor the head adjusted itself to the optimum diameters and finally engaged in the R.O.P. position as illustrated. It may be said that the rounded surfaces of the fetal head sliding easily against the curvatures of the inlet results in adjustment of the head in a position which offers the least resistance to its engagement.

Although this is not an example of internal rotation, it serves to illustrate a form of simple rotation at the brim, better referred to as adjustment. It simply means that the head, meeting obstruction, is forced along the path of least resistance. Now, to some extent, we are dealing with the same conditions at the interspinous level where internal rotation most often takes place, although the factors which resist and those which favor rotation are more involved.

In Fig. 5 we note an example of internal rotation. The fetus descended in the transverse position R.O.T. to the level of the spines, and because the prominent spines offered resistance in front while the sacrum was directed well backward, we find the occiput moving into the roomy posterior segment to become a secondary right occipitoposterior position. The head in this case did not rotate to a posterior position according to West's theory, because it was extended since it was partially flexed. It apparently rotated posteriorly, because there was more room for the occiput in that part of the midpelvis than there was anteriorly. Internal rotation, therefore, is influenced to a large extent by the shape of the pelvis.

To state the facts about internal rotation briefly it may be said that under the influence of the inclined planes of the pelvic gutter which initiate the mechanism, the vertex will tend to turn anteriorly when the head reaches the pelvic floor in an oblique anterior position and conversely will tend to turn directly posteriorly when the head reaches the pelvic floor in an oblique posterior position, if the pelvis permits. The inclined planes of the pelvic floor therefore while responsible for rotation do not determine in what direction rotation will occur. According to this concept of internal rotation when the head reaches the pelvic floor in an obliquely posterior position, it will always tend to rotate directly posterior. In the average case, however, such rotation is resisted by the sacrum and the strong sacrospinous ligaments and occurs only when the lower sacrum is well backward and has an ample concavity as well. This was an observed fact in practically all the cases of direct occipitoposterior rotation in this series. Under these circumstances even a fairly large head may rotate posteriorly and in the presence of an average sacral inclination, a small child may also rotate in this way. This explains why so many small babies become direct occipitoposteriors.

In addition to these sacral characteristics, posterior rotation to the hollow of the sacrum requires that the upper pelvis have a sufficiently long A.P. diameter to accommodate the brow which is considerably in advance of the occiput when the head is extended.

We next inquire into what happens when, by virtue of the resistance offered by the sacrum and the sacral ligaments and muscles, the obliquely posterior vertex cannot follow its natural inclination to rotate further in that direction to become a direct occipitoposterior. Suppose we first assume that the head will simply attempt to descend further in the oblique O.P. without rotational change of direction. Now it can be easily demonstrated that if a fetal head is placed in the pelvis as an oblique posterior in a partially deflexed attitude as they invariably occur and an attempt is made to push the head downward in this position, say an R.O.P., it will be found that the face or the brow of the child comes in contact with the left fore pelvic brim which prevents it from proceeding further in this direction (Fig. 6). So we may conclude that under the conditions previously mentioned the head moves downward in an oblique O.P. until the brow meets with resistance at the brim at which point the brow slides backward along the pelvic brim, again following the path of least resist-

ance in a manner similar to the mechanism of "adjustment" previously discussed. This, of course, makes the occiput turn forward to a transverse position. From this transverse position, the occiput will then move forward and downward on the inclined planes of the pelvic floor to the anterior position provided again that the shape of the pelvis permits. If the brim is transversely narrowed, as in an anthropoid pelvis, it may be impossible for the brow to move backward and a posterior arrest is the result (Fig. 7). It must be noted, however, that while conditions may be favorable for backward rotation of the brow at the brim there

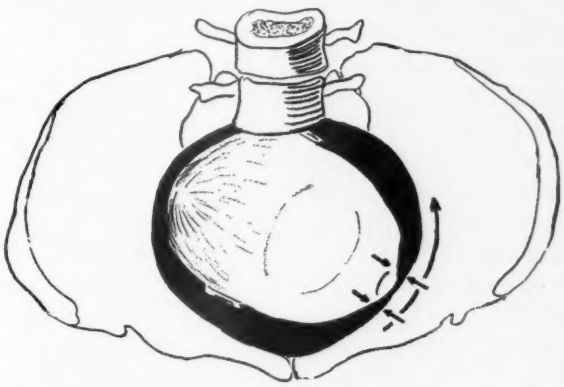


Fig. 6.—If the partially extended oblique posterior were to continue its descent without change of direction, the facial aspect of the head would meet obstruction in the fore pelvis as indicated by the arrows.

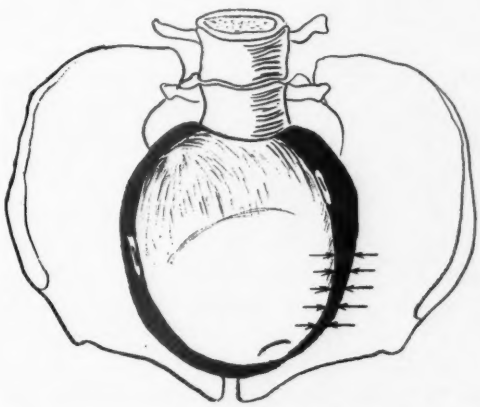
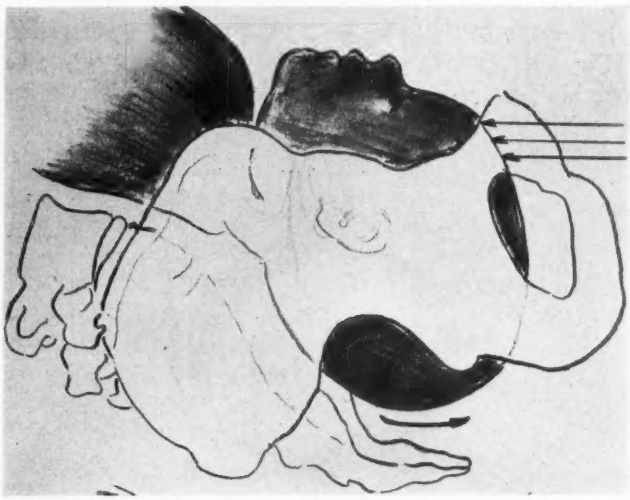


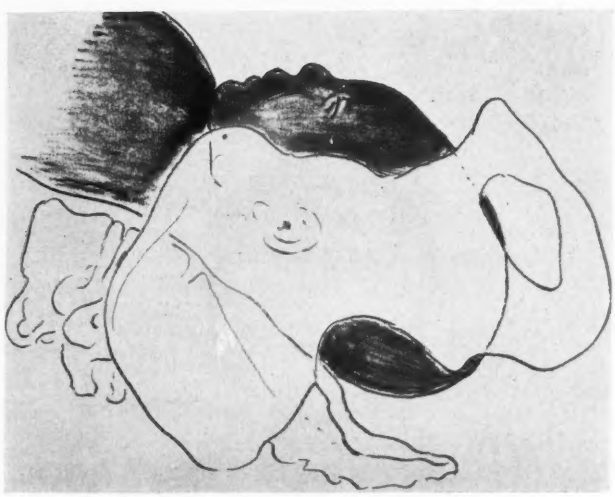
Fig. 7.—A narrow pelvic brim may be the cause of failure of rotation in a posterior position and cause it to become arrested.

may be obstruction to forward rotation of the occiput by prominent spines or convergence of the lateral walls of the pelvis (Fig. 9). It may be said, therefore, that rotation toward the front in a posterior position will occur when the head is forced away from the limiting posterior boundaries of the sacrum providing that the relations of the brow or face to the brim and those of the occiput to the spines and side walls of the pelvis permit.

To return to those posterior arrests that are caused by a narrow brim preventing rotation (Fig. 7), the detailed study of the mechanism in those cases shows that they may correct themselves by a mechanism of flexion. If the forces of descent continue, then flexion occurs, because while the resistance of the face or brow against the upper fore pelvis



A.



B.

Fig. 8.—Failure of rotation caused by narrow pelvic brim as in Fig. 7 may correct itself by a mechanism of flexion. Forepelvic obstruction (arrows) is relieved by flexion and head is allowed to rotate.

holds the upper part of the vertex fixed, the occiput is being forced downward away from the sacrum. This forward excursion of the occiput results not only in flexion but also eventually in a recession of the brow from the narrow fore pelvis. As a result of these changes, further

progress may be expected because the impaction of the brow on the upper pelvis is relieved and this allows the brow to rotate backward slightly while concomitantly the occiput moves forward and downward. By virtue of this seesaw action of the head (Fig. 8), the upper brow moving away from the fore pelvis and consequently being enabled to slide backward, rotation may eventually take place if the brim is not excessively narrow.

Flexion is of added advantage and further aids this mechanism because it changes the cranial girdle of contact from the occipitofrontal plane to the suboccipitobregmatic plane so that the cross section of the fetal head within the brim is changed from a long oval to a circle.

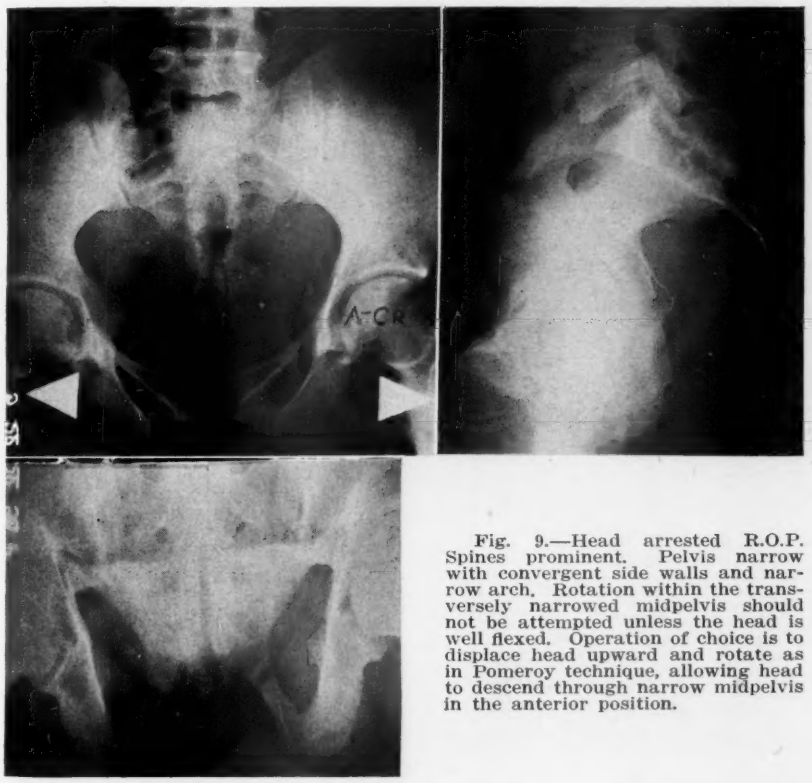


Fig. 9.—Head arrested R.O.P. Spines prominent. Pelvis narrow with convergent side walls and narrow arch. Rotation within the transversely narrowed midpelvis should not be attempted unless the head is well flexed. Operation of choice is to displace head upward and rotate as in Pomeroy technique, allowing head to descend through narrow midpelvis in the anterior position.

This type of arrest then is due primarily to the fact that the brim, being transversely narrowed, does not easily permit that part of the head which is still within it to turn. Since a cross section of the plane of the vertex that is within the brim is a long oval and coincides with the shape of the brim and since it is impossible to turn one long oval within another oval which it closely fits, a change of conditions must be set up if delivery is to be accomplished. We have just seen that this may occur spontaneously by a mechanism of flexion and this might be the first maneuver that suggests itself. Unfortunately manual attempts to bring this about often fail because we cannot always do with the hand what nature accomplishes only after hours of tedious labor if at all.

If labor must be terminated it becomes most important to recognize the relationship between the long oval of the head and the long oval of the inlet and realize that rotation cannot be accomplished at the level of arrest. Displacement of the head upward as in a version or as recommended by Pomeroy becomes the method of choice in those cases.

Another form of arrest is that which results from the fact that the occiput cannot rotate forward because of prominent spines. These cases arrest in the R.O.P. position and must be handled according to the type of pelvis in which the prominent spines are found. When the narrow

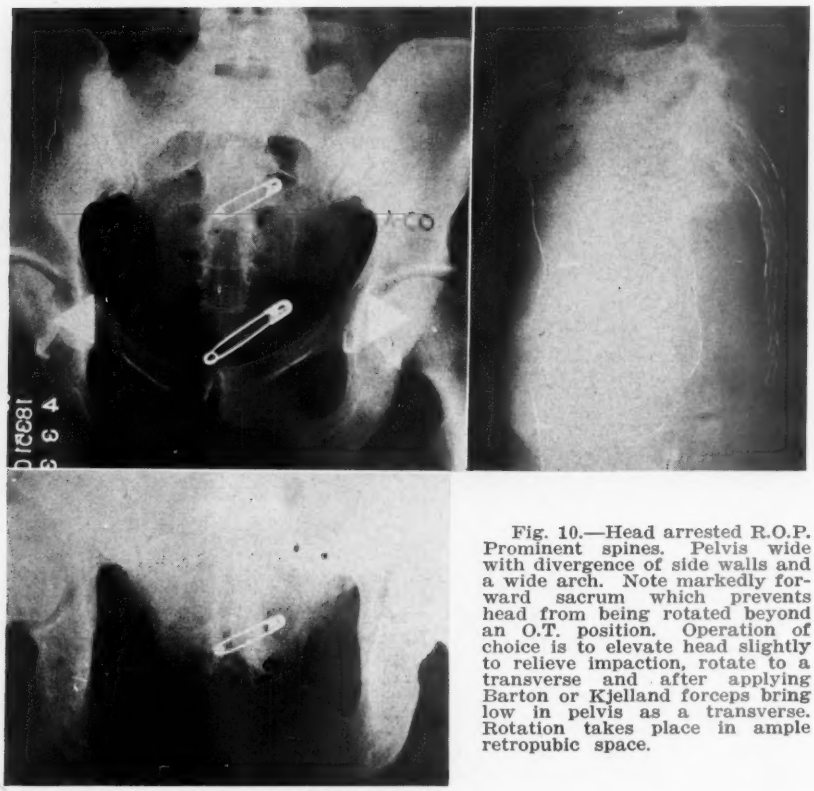


Fig. 10.—Head arrested R.O.P. Prominent spines. Pelvis wide with divergence of side walls and a wide arch. Note markedly forward sacrum which prevents head from being rotated beyond an O.T. position. Operation of choice is to elevate head slightly to relieve impaction, rotate to a transverse and after applying Barton or Kjelland forceps bring low in pelvis as a transverse. Rotation takes place in ample retropubic space.

spines are associated with a general narrowing of the entire pelvis (Fig. 9), the head must be pushed up, free of the brim, and rotated and brought down in an anterior position. On the other hand, when the prominent spines are associated with a pelvis that has a flat posterior segment (Fig. 10), the head can be manually rotated to an O.T. position after lifting it slightly above the level of impaction against the spines and since the flat posterior segment will not allow it to go any further than an O.T., Barton or Kjelland forceps are applied to the head in this position. Then, by lateral flexion, the head is brought into the retropubic space away from the spines where low rotation can be accomplished. This technique, however, requires good transverse width in

front of the spines to allow the head to be brought down into the retropubic space as a transverse.

These oblique occipitoposterior arrests in contrast to direct occipitoposterior arrests may be seriously mishandled by attempting to pull the head down in the posterior position. The fact that the head remains obliquely O.P. and does not rotate directly posterior is evidence of

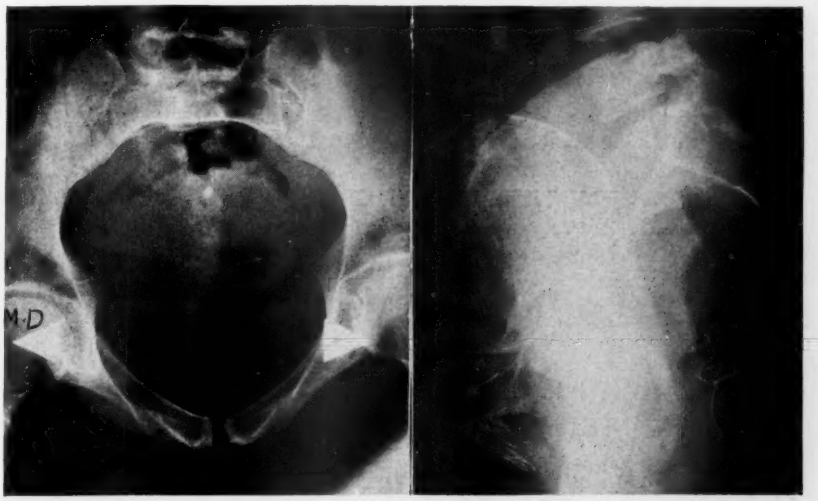


Fig. 11.—Case illustrates why oblique posterior arrests should not be brought down in the posterior. Manual rotation and Scanzoni failed due to transverse narrowing, then brought down O.P. with injury of sacral plexus and abrasion of child's forehead. An oblique posterior arrest in itself is evidence of restricted space posteriorly. Displacement upward and rotation above brim should have been procedure of choice.

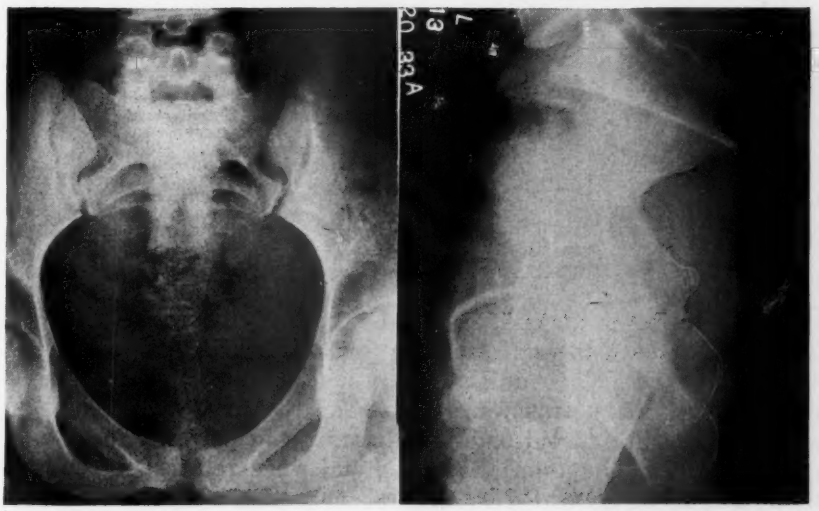


Fig. 12.—Direct occipitoposterior arrest. Direct occipitoposteriors give evidence of sacral ampleness at the level of the spines but not necessarily below that. Forward sacral tip does not permit traction of head in direct posterior. Manual rotation usually easy because head is low and usually well flexed.

sacral resistance and traction in the posterior position may result in injury to both mother and child (see legend Fig. 11).

A word should be said about those cases that rotate directly posterior (Fig. 12). While it has been previously stated that they represent evidence of ampleness of the sacral concavity and of the posterior sagittal diameter at the level of the spines, the sacral tip may come forward and so cause a direct O.P. arrest low in the pelvis. This type of arrest is usually handled quite easily by manual rotation to an O.A., for the head is low and flexed so that rotation is usually easy. Whether the sacrum encroaches or not, it does not seem justifiable to deliver direct O.P. arrests face-to-pubis, except in the very occasional case in which there is more room in the posterior sagittal diameter than the average.

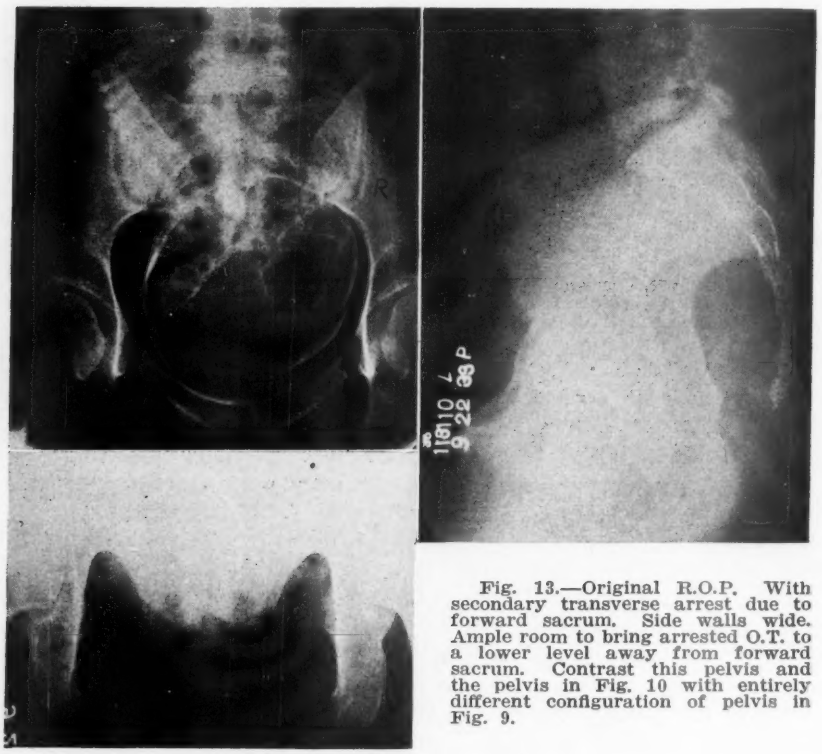


Fig. 13.—Original R.O.P. With secondary transverse arrest due to forward sacrum. Side walls wide. Ample room to bring arrested O.T. to a lower level away from forward sacrum. Contrast this pelvis and the pelvis in Fig. 10 with entirely different configuration of pelvis in Fig. 9.

After rotating to an O.T. the head may fail to rotate further. The failure of the head to rotate further than a transverse may be due to: (1) An inlet with flattening in the posterior segment; (2) a forward sacrum. Secondary transverse arrests of the first variety most frequently occur in android or android-anthropoid pelves. The head engages in the occipitoposterior position and when rotation to the hollow of the sacrum is prevented by the resistance of the sacrum behind, the occiput rotates forward but frequently becomes arrested part way and remains as an occipitotransverse; the flattening of the pelvic brim has prevented it from turning further. The flat posterior segment of the

inlet in these cases exerts an effect which is comparable to the transversely contracted inlet in the oblique posterior arrests. Rotation can take place only after the head has descended lower in the transverse so that the obstruction caused by the posterior flattening of the pelvis is cleared. In Fig. 13 the original presentation was R.O.P. It became arrested in the R.O.T. position and while it should have been brought down lower in this position, it was unfortunately pushed up, rotated to a direct anterior, and delivered as such with a great deal of difficulty. The child survived although it was a shocking type of delivery. Here we note that the Pomeroy principle of rotation, so ideally suited in the transversely narrowed pelvis, becomes undesirable because the contours of the pelvis demand an entirely different mechanism.

It is obvious, therefore, that these transverse arrests of an original posterior position, referred to as deep transverse arrests when they occur low in the pelvis, may be explained by the architecture of the pelvis. Actually these cases give evidence that a correct mechanism is being naturally followed, the low transverse position being maintained by the flat posterior segment of the inlet or a forward sacrum in the presence of ample transverse diameters. Nature seems to point the way. Traction in the transverse with lateral flexion into the lower retropubic space where rotation is brought about is the usual method of choice. These cases are more difficult to interpret when arrest takes place at a higher level in the pelvis when the vertex is still in the obliquely posterior position. The transverse mechanism that should obtain in the lower pelvis has not been indicated by the position of the head and can be determined only after a complete appraisal of the entire pelvic architecture.

The various mechanical principles that have been applied to the operative treatment of the difficult types of arrests under discussion are of considerably more importance when the head is extended and unmolded than when the head is flexed and well molded. In the well-flexed head all the cross sections throughout the entire head at right angles to the axis of descent become spheroids which meet with equal resistance no matter how the head is turned. But in the majority of posteriors that become arrested, such flexion is not complete and for this reason the presenting anteroposterior diameters of the fetal head are longer than the transverse diameters. Since it has been shown that the pelvic types in which posteriors may occur vary markedly in the ratio between their available anteroposterior and transverse diameters at all pelvic levels, it naturally follows that each posterior arrest requires correct adaptation of the longer cephalic diameters to the correspondingly longer pelvic diameters.

SUMMARY

1. The occipitoposterior position in the main is caused by the adaptation of the head to a pelvis having a narrow fore pelvis and an ample anteroposterior diameter and therefore may be considered "physiologic."

2. Degrees of the posterior position can be differentiated. A true posterior position is one in which the occiput is at or posterior to the sacroiliac synchondrosis.

3. Occipitoposterior positions, although physiologic and in spite of the fact that 70 per cent deliver spontaneously, cause more dystocia than the other vertex positions.

4. Dystocia in posterior positions originates with the abnormality of the pelvis in which they occur.

5. Extension is a common feature of the posterior mechanism and is caused by the posterior axis of fetal drive. Extension not only results in larger presenting diameters but also causes a part of the uterine drive to be dissipated.

6. Flexion greatly facilitates the mechanism and should be encouraged by posture. A forward excursion of the fetal axis must take place before flexion can occur.

7. Internal rotation although receiving its impulse from the inclined planes of the pelvic floor receives its directional force from the variable resistances offered by the bony pelvis in all the pelvic planes through which the head is descending.

8. Since the pelvic architecture shows marked variations in shape, it follows that the patterns of rotation show corresponding variations.

9. Emphasis is placed on the importance of recognizing two fundamentally different pelvic forms frequently associated with posterior positions, viz., those forms in which the transverse diameters are contracted at the brim or midpelvis or at both levels with compensating ampleness in the anteroposterior diameters and the converse of this form in which the anteroposterior diameters are shortened by virtue of a flat posterior segment at the brim or a forward sacrum at the midpelvis level while the transverse diameters remain ample. It follows that operative techniques should be individualized for each type.

10. The occipitoposterior mechanisms which have been reviewed may be translated into operative principles as follows:

a. When the posterior arrest is due to a narrow anthropoid pelvic brim preventing rotation, the head is pushed up and rotated above the brim. Version is also correct in principle.

b. When arrest is due to narrow spines in definite anthropoid types, the head is pushed up and rotated above the spines or above the brim. Version is also an alternative procedure.

c. When the posterior aspect of the inlet is flat or the sacrum is forward, rotation is carried to the transverse only and in this position the head is brought into the lower fore pelvis or the retropubic space thereby converting it into a deep transverse. Rotation is carried out at this low level. Upward displacement of head with rotation and version are incorrect procedures.

d. When the posterior aspect of the inlet is flat or the sacrum is forward and labor has progressed sufficiently to allow a deep transverse arrest to occur rotation is again carried out at a low level just behind the pubis.

e. When the head is arrested in a direct occipitoposterior, deliver without rotation only when the lower sacrum is not encroaching. In most cases the head should be rotated to the anterior. Such rotation is carried out at the level which is most suitable for the pelvis in which it occurs.

f. When the head is low, well-molded, and well-flexed manual rotation is the most desirable procedure.

g. Rotation at level of arrest is rarely a procedure of choice because in most instances there is some pelvic obstruction which is preventing rotation at that level.

h. The unmodified Scanzoni maneuver with simultaneous traction and rotation initiates the act of rotation at the level of arrest where there is obstruction. It is, therefore, an undesirable procedure in those cases which have a well-molded and flexed head. Even in this group of cases manual rotation is the operation of choice.

I wish to acknowledge my deep appreciation for the many helpful suggestions offered by Dr. W. E. Caldwell in the course of this study.

THE CLINICAL APPLICATION OF ROENTGEN PELVIMETRY AND A STUDY OF THE RESULTS IN 1,100 WHITE WOMEN*

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WITHIN the past decade the application of roentgen techniques to the study of the female bony pelvis has resulted in a definite revision of our views concerning the conformation of this structure and its relation to the process of childbirth. As a result of roentgen studies in adolescents and adults, we now possess certain knowledge of pelvic variations and this information permits their adequate description and ready identification. A comprehension of this newer knowledge is of importance to the obstetrician, for he will find advantages in applying it to many of his clinical problems.

It is the purpose of this paper to endeavor to clarify the subject, to review its more important aspects and to survey certain data obtained from the study of a comparatively large group of primiparous patients in whom a roentgen survey of the pelvis has been made.

THE PELVIS AS A WHOLE

It is important in considering the pelvis as a whole to consider some of the fundamentals of pelvic architecture. The pelvis of the newborn shows essential differences from that of the adult. In the former the pelvis is relatively longer anteroposteriorly and relatively shorter transversely. This applies to the entire bony pelvic canal throughout its course from inlet to outlet. During growth through childhood and particularly during adolescence, certain changes in these anteroposterior and transverse relationships usually take place. In some individuals such changes are relatively extensive, the anteroposterior relationships becoming definitely shortened while the transverse relationships become relatively longer. In other individuals such changes are less extensive, and in many individuals these anteroposterior

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and transverse relationships remain not greatly changed, the general appearance resembling the conformation of that seen in childhood. Thus, we find variations in the adult pelvis, and in general these variations are: (a) those whose essential anteroposterior diameters are relatively longer than the transverse diameters, (b) intermediary states, and (c) those whose essential transverse diameters are relatively longer than the anteroposterior (Figs. 1 to 4).

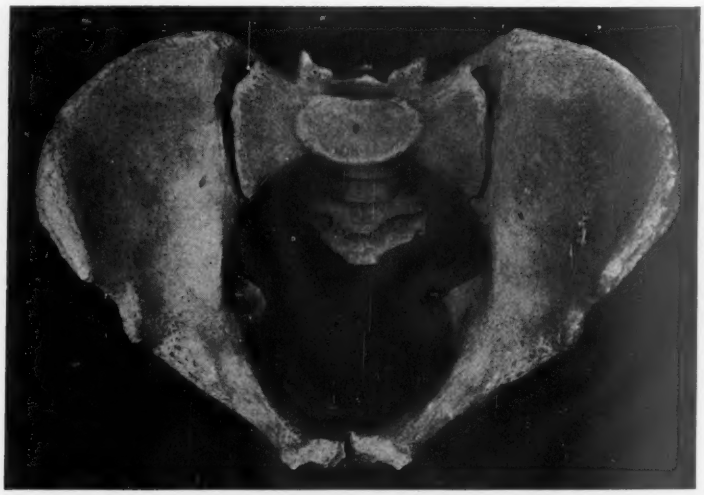

Fig. 1.—Dolichopellic type: anteroposterior of inlet, 12.5 cm.; transverse of inlet, 11.8 cm. (Male pelvis.)

Fig. 2.—Mesatipellic type: anteroposterior of inlet, 11.3 cm.; transverse of inlet, 12.3 cm.

These changes in anteroposterior and transverse relationships probably result from the influence of various factors: hormonal, hereditary, environmental, and mechanical. Just what part the first two play may be only conjectured, but the force of environment in influencing pelvic

architecture is definitely seen in the well-known changes due to rachitic influence. The influence of an environmental factor is also strongly suggested in our comparative studies in women of the college group and those of the clinic group.[1] The mechanical factors are those related to posture, muscular action, etc.

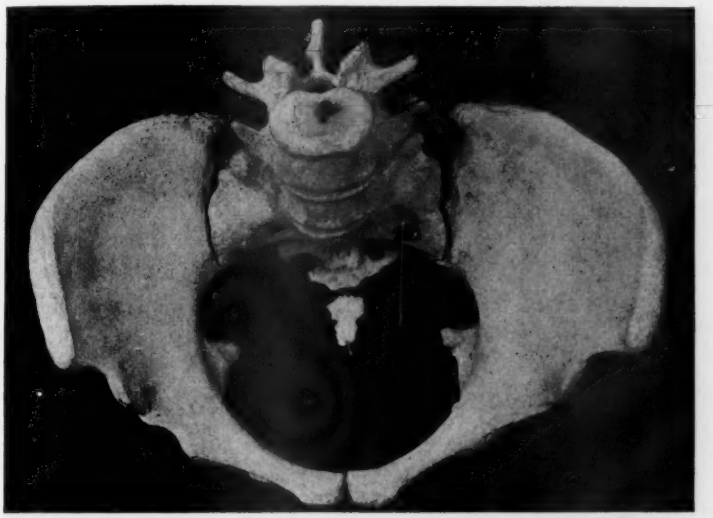

Fig. 3.—Brachypellic type: anteroposterior of inlet, 9.8 cm.; transverse of inlet, 12.4 cm.

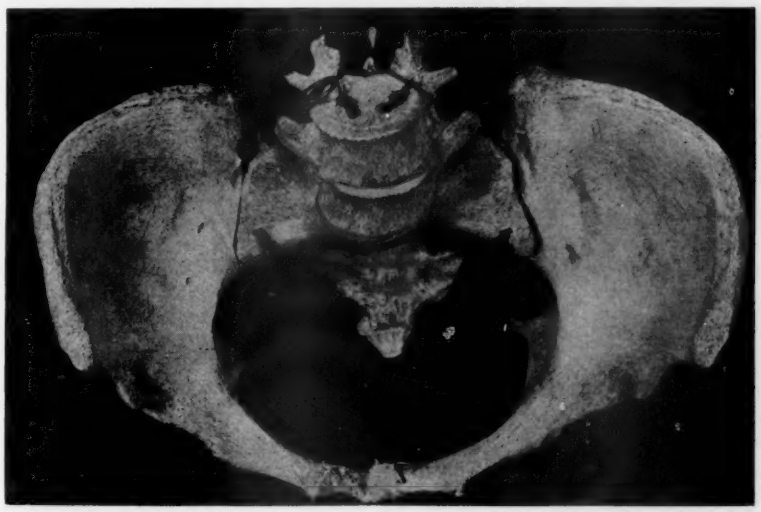

Fig. 4.—Platypellic type: anteroposterior of inlet, 10.0 cm.; transverse of inlet, 14.7 cm.

As stated above, the shape of the pelvic inlet in early childhood is characteristically elongated anteroposteriorly, or dolichopellic, and if a pelvis of this type were to grow symmetrically, it would obviously have a similar shape in adult life. From this it would appear that the round or

flattened forms of pelvic inlet may arise as a result of either of two mechanisms; an excessive growth laterally that is of the transverse diameter or a diminished growth anteroposteriorly. A comparison of the mean dimensions of the inlet from the various types in our series sheds some light on this question.

MEAN VALUE FOR DOLICHOPELLIC	MEAN DIFFERENCE AS COMPARED WITH DOLICHOPELLIC		
	MESATIPELLIC	BRACHYPELLIC	PLATYPELLIC
Anteroposterior 12.59 cm.	−0.73	−1.52	−3.24
Transverse 11.92 cm.	+0.46	+0.89	+0.86

Thus, it seems apparent that the lessening or incomplete development of the anteroposterior diameter is the more important mechanism, and increasingly so as the degree of flattening becomes more extreme.

For purposes of the classification of pelves to be discussed later, we may say that the tendency of a pelvis to retain most of the relationships of fetal and childhood conformation and thus remain relatively "elongated" anteroposteriorly may be spoken of as dolichopellism (dolicho-long), while the tendency in a pelvis to become relatively broader transversely and short anteroposteriorly is that toward platypellism (platy—broad or flat).

MALE AND FEMALE PELVES

Although, as we have shown,[2] the same general variations occur in the adult pelves of both sexes, there do occur in both certain differences which are designated as sex characteristics. An understanding of the essential sexual differences between male and female pelves may be tabulated as follows:

MALE	FEMALE
Heavier, rougher, more massive bones	Greater size, lighter build
Lessened capacity of pelvic inlet	Greater capacity of pelvic inlet
Narrower pubic arch, more angular	Greater width of pubic arch
Sidewalls converge	Larger interischial width
Smaller notch. Boundaries meet above in acute angle	Great sacrosciatic notch, large, almost rectangular
Sacrum placed more anteriorly toward pelvic axis	Sacrum placed more posterior to pelvic axis
Pelvic height greater	Pelvic height less

It has been shown that certain characters resembling those seen in male pelves may occur in female pelves, and when this happens such changes may have definite obstetric significance. These characters in general may be stated:

1. Long narrow sacrosciatic notch with sacrum in a more forward position lessening the space in the posterior pelvis.
2. Narrow subpubic angle and lessened transverse diameter of outlet.
3. Convergence of pelvic sidewalls from above downward restricting room in mid and lower pelvis.
4. A tendency toward angulation in the inlet at or near the sacroiliac junction with a somewhat posterior displacement of the transverse diameter.

Narrowing of the forepart of the pelvic inlet has been described by some authors as a definite male characteristic, and I agree that this is seen in many male pelves, but it is by no means constant, for the majority of the pelves in our study of adult males showed a forepart as wide relatively as that seen in female pelves. Again it should be emphasized that in neither male nor female pelves can the conception of general conformation be said to be concrete, for much the same variations are found in both sexes.

PELVIC PLANES AND CONTOURS

When we consider the bony pelvis and, in particular, the birth canal, it is at once obvious that we are dealing with an intricate structure. Furthermore, inasmuch as the entire birth canal is involved in the process of birth, it must be studied obstetrically as a whole and not segmentally. This does not mean that a concept of certain planes and contours is not of essential use for purposes of description and for the estimation of pelvic capacity. For this purpose a simplification of the problem becomes possible by considering three portions of the pelvis; viz., the pelvic inlet, the pelvic outlet and the pelvic sidewalls. A consideration of these will furnish information which will be of distinct advantage in estimating pelvic capacity and in describing pelves (see Figs. 5 and 6).

THE PLANE OF THE PELVIC INLET

In considering the pelvic inlet, we describe this portion of the pelvis as follows:

From the obstetric point of view this plane is bounded anteriorly by the upper posterior surface of the symphysis and the forward portions of the iliopectineal lines, laterally by the iliopectineal lines and posteriorly by the posterior portions of these lines and the anterior upper surface of the sacrum at the point where the convergence of these lines takes place. (This point may or may not be located at the sacral promontory.) The essential diameters of this plane are:

1. *The anteroposterior diameter* extending from a point on the posterior surface of the symphysis, 1 cm. below its superior border, to the anterior surface of the upper sacrum at the point where the iliopectineal lines would meet were they to be extended.

2. *The transverse diameter* being the widest distance separating the iliopectineal lines.

3. *The posterior sagittal diameter,* which is that portion of the anteroposterior diameter which lies posterior to its point of intersection by the transverse diameter. The length of this diameter is a good index to the amount of space in the upper posterior pelvis and also gives some information as to the shape of the plane of the inlet, for when shortened it means a posterior displacement of the transverse diameter.

In considering the plane of pelvic inlet, as outlined, any abnormalities should be noted with regard to symmetry and to the configuration of its anterior and posterior segments. When the anterior segment is narrowed or angular, this fact may have definite obstetric significance.

THE MIDPELVIC PLANE

This plane, somewhat ovoid in form, is large anteriorly and somewhat restricted posteriorly, being narrowed by the convergence of the sacrosciatic ligaments. It is bounded anteriorly by the lower border of the symphysis, laterally by the ischial spines, and posteriorly by the lower third of the sacrum, usually at the junction of the fourth and fifth sacral segments. Three diameters are of obstetric significance:

1. The anteroposterior diameter
2. The transverse or bispinous diameter
3. The posterior sagittal diameter

The anteroposterior diameter: From a point on the lower border of the symphysis this diameter extends posteriorly at the level of the ischial spines, usually falling to a point at or near the junction of the fourth and fifth sacral vertebras.

The transverse diameter is the narrowest distance separating the ischial spines.

The posterior sagittal diameter is that part of the anteroposterior diameter which lies posterior to its intersection by the transverse diameter.

THE PELVIC OUTLET

It must be remembered that the pelvic outlet consists essentially of two planes represented by two triangles, the bases of which join each other at the lowermost points of the tubera ischii. For many years a bituberal diameter has been described and used as an index to outlet capacity, and extending posteriorly from a midpoint on this diameter a posterior sagittal diameter of the outlet has also been described. At the present time I am convinced that the mensuration of the so-called bituberal diameter is so variable that definite measurement by either palpatory or roentgen methods is very questionable. This is because of a lack of definite end points. It is, indeed, true that contractions of the outlet and narrowing of the tubera ischii may and should be recognized clinically by palpation, but the mensuration of such contraction in terms of a bituberal diameter is difficult of proper determination. For this reason I recommend the employment of the so-called widest diameter of the outlet as described by Caldwell, Moloy and D'Esopo.[3] It is possible to determine this measurement with considerable exactness by roentgen methods and, taken in conjunction with the palpatory evaluation referred to, it should serve as a good index to pelvic capacity in this portion of the pelvis (see Dimension E, Fig. 5).

Another dimension which has interested us recently is that known as pelvic height or depth. Schuman,[4] in 1934, pointed out the value of this dimension, stating that clinically the most important characteristic of the male, funnel or high assimilation pelvis is its increased depth. This dimension is the perpendicular distance from the tuberosity of the ischium to the iliopectinal line. Schuman designated this as "the pubotuberous diameter" (see Dimension E, Fig. 6). This author quotes Todd's results in 53 white male and 50 white female pelves with averages of 101 mm. and 90 mm., respectively. In a series measured roentgeno-

logically by myself, the average for 61 males was 101.9 mm. and that for 92 females, 88.8 mm. Schuman recommends external measurement with a caliper pelvimeter and subtracts from 1 to 2 cm. for the thickness of the soft parts. I find that this measurement may be readily and satisfactorily made roentgenologically on the lateral film by a technique to be described later.

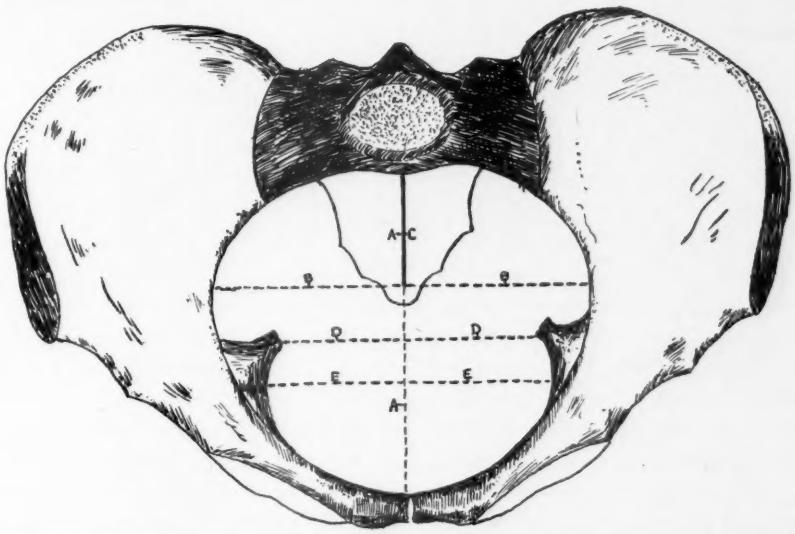

Fig. 5.—The pelvis as seen from above. The various diameters are shown. *A*, Anteroposterior diameter of inlet; *B*, transverse diameter of inlet; *C*, posterior sagittal diameter of inlet; *D*, bispinous or transverse diameter of midplane; *E*, widest transverse diameter of outlet.

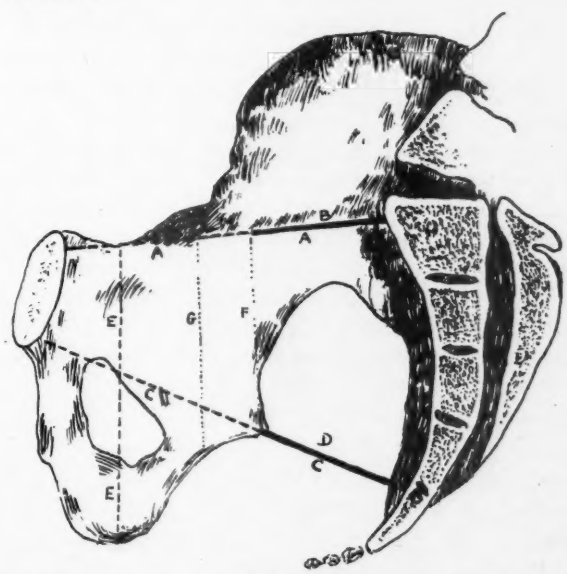

Fig. 6.—Lateral aspect of pelvis. Diameters and distances establishing levels are shown. *A*, Anteroposterior diameter of inlet; *B*, posterior sagittal diameter of inlet; *C*, anteroposterior diameter of midplane; *D*, posterior sagittal diameter of midplane; *E*, pubotuberous diameter; *F*, distance establishing level of ischial spines; *G*, distance establishing level of widest transverse diameter of outlet.

SUMMARY OF MANEUVERS FOR PELVIC ESTIMATION

Thus far we have spoken of eight diameters which we may consider as the *cardinal diameters of the pelvis* all of which may be measured satisfactorily by roentgen means. It is useful here to point out certain general information which we should also seek in the evaluation of pelvic capacity. A good deal of such information may be secured by manual examination and inspection of the patient. A consideration of the gait, general constitution, and shape of Michaelis' rhomboid is of value. By vaginal and rectal examination much can be learned if the observer keeps in mind the possibilities and limitations of these maneuvers. Palpation of the pubic arch, the determination of the downward course of the pubic rami, the width of the tubera ischii should be noted and recorded. Vaginal examination should include the palpation of the ischial spines, their relation to the anterior surface of the sacrum, and the course of the sacral curve from above downward. An attempt should be made to evaluate whether or not the pelvic sidewalls converge more than usual in the lower pelvic space. The determination of the diagonal conjugate as described in textbooks does not serve any useful purpose as long as roentgen pelvimetry is to be carried out. Indeed, I am convinced that, even when roentgen determinations are not done, the time-honored determination of the diagonal conjugate diameter in some instances actually may be misleading. This is because of the great variation in the position of the sacral promontory in its relation to the true pelvic inlet. (This fact should be remembered by those who advocate the determination of the diagonal conjugate diameter as a criterion for the performance of roentgen pelvimetry in the individual case.) The rectal examination for determining the relationship of the ischial spines to the lower sacrum is a useful and important maneuver. Both rectal and vaginal examinations are important adjuncts in determining pelvic capacity.

Let us now consider the application of roentgen techniques to the visualization and mensuration of the pelvis. For this purpose I recommend for routine purposes the taking of two flat films consisting of one view of the pelvic inlet looking down into the pelvic cavity, which is spoken of as the inlet view, and the other depicting the lateral aspect of the pelvis. Obviously, in individual cases because of abnormalities or for purposes of study during labor, other views may be useful, and in this latter instance stereoscopic views may serve a very useful purpose. For routine pelvimetry the two views of which I have spoken appear entirely adequate, for all of the cardinal diameters may be measured and all of the important pelvic aspects may be studied. The techniques used in placing the patient in position will be described later. The inlet and lateral views are both taken at a 36 in. target film distance. This distance is kept uniform for two very important reasons. (1) *If films are always produced under this condition, the relative size values in comparing films will always be more or less constant, and in studying the pelvis as a whole this fact is very useful.* (2) *By using a 36 in. target film distance distortion due to spread of rays is minimized.*

Having obtained an inlet view of the pelvis on a flat film, we should first study the bony pelvic relationships as a whole. The symmetry or asymmetry of the pelvis from above downward is readily determined. The general shape of the inlet is seen and the position of the pelvic sidewalls, ischial spines, etc., are depicted with clarity. The various forms of pelvic variation and the presence of certain malelike characters become readily apparent in this view. In the lateral view we note the height of the pelvis, the curve of the sacrum, the character of the notch, the thickness and inclination of the symphysis and the position of the sacral promontory in its relation to the pelvic inlet. As in the inlet view the pelvis is studied, also, as a whole from this aspect. It is, however, important to take certain pelvic measurements to supplement this information and to further determine the capacity of the pelvis.

PELVIC MENSURATION

With regard to pelvic measurements per se it should be emphasized that, valuable as they are, they are by no means the sole criteria upon which obstetric prognosis should be based. Such determinations form the basis for a practical classification of pelvis and also are an important index of pelvic capacity. To those who think that pelvic measurements have but academic interest I would point out the truth of Lord Kelvin's dictum that, "When you can measure what you are speaking about and express it in numbers you know something about it, but when you cannot measure it, when you cannot express it in numbers your knowledge is of a meagre and unsatisfactory kind."

In making flat films of the pelvic inlet and the lateral pelvic aspect, it is clear that for purposes of proper mensuration, correction of the distortion due to the spread of the roentgen ray must be made. It is also obvious that if we can identify in space any plane to be measured and its position relative to the target, this distortion may be compensated for. This is done by means of the lead grid and upright rod to be described later.

As stated before, for routine pelvimetry we insist upon two views, one lateral and one pelvic inlet projection. Both views are necessary for the proper survey of the pelvis, and, furthermore, each view becomes an excellent check upon the other, as the anteroposterior diameter of the inlet may be measured in both.

ROENTGEN TECHNIQUE FOR ROUTINE PELVIMETRY

The technique which we are at present using has been recently described by H. M. Wilson and myself[5] and is here reprinted in detail. It represents a slight change in the lead grid from that which we have previously used, and this has been made in order that in the inlet view the transverse diameters of levels other than that of the pelvic inlet may be measured. However, in both these inlet and lateral techniques the fundamental principle remains unchanged.

Our routine is to take the lateral projection first and this may be described as follows:

1. The patient removes her clothing, putting on heelless slippers and the usual hospital bed gown open at the back.

2. She is placed standing in front of an erect Bucky diaphragm or an adjustable cassette changer, such as is used for chest work, with either the right or left lateral aspect of the body toward the target. The arms are folded across the chest.

3. The target film distance is 36 inches and the target is centered just below a point on the external conjugate diameter one-third the distance from the symphysis pubis to the depression under the fifth lumbar vertebra.

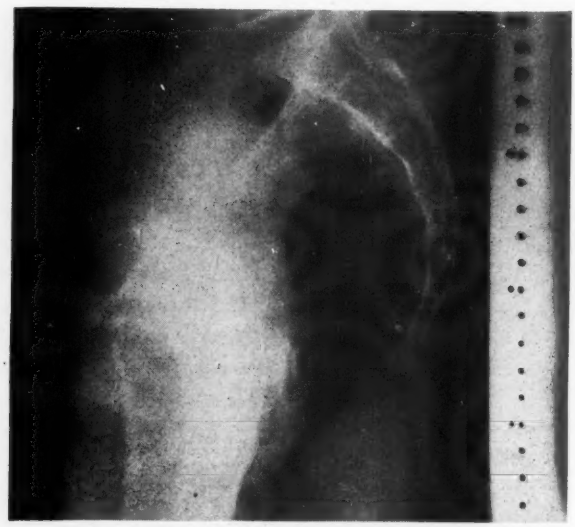

Fig. 7.—Lateral roentgenogram. Compare with Fig. 6. The scale represents corrected centimeters in the midplane of the body. By means of calipers the various dimensions depicted in Fig. 6 may be measured. The lateral morphologic aspects are readily visualized.

4. A binder is placed around the patient and attached to the cassette changer to insure further steadiness during the exposure.

5. Before the exposure is made, an upright metal rod (lead and iron) with a centimeter scale perforated in a lead strip is placed posterior to the patient close to the fold of the nates.

6. The time of exposure varies with the thickness of the patient, all other factors being constant; in general the time is from seven to twelve seconds.

Comment on Lateral Technique.—When developed and viewed (Fig. 7) the following landmarks should be readily identified: anterior and posterior borders of the symphysis pubis, acetabula, ischial spines, ischial tuberosities, the lower lumbar vertebrae, the promontory and anterior surface of the sacrum, and the sacrosciatic notch. On one edge of the film may be seen the shadows cast by the perforations giving corrected centimeters in the sagittal plane of the patient. By means of calipers, using this scale, any diameters in this plane may be measured.

The advantages of this lateral technique may be summarized as follows:

1. All the anteroposterior diameters of the bony pelvis may be measured, including those of the pelvic inlet and midpelvis.

2. The level of the ischial spines and the level of the lower inner surface of the ischial tuberosities may be determined in this view.

3. The contours of the anterior surface of the sacrum may be studied, a matter of importance in the recognition of sacral abnormalities, especially those due to the influence of rickets.

4. When lateral roentgenograms are made at term or in labor, the relation of the presenting part to the superior strait may be studied with advantage.

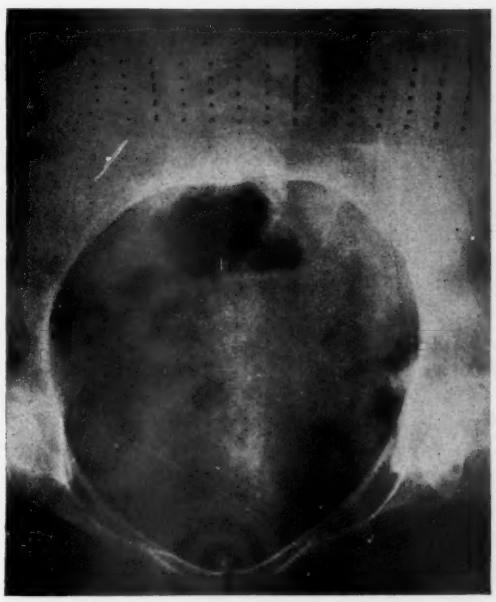

Fig. 8.—Pelvic inlet roentgenogram. Compare with Fig. 5. The scale represents corrected centimeters for various levels of the pelvic canal. The top line is used for measuring the diameters of the inlet. The other levels are established on the lateral roentgenogram (see text). Pelvic morphology is readily established by viewing both lateral and inlet views.

A recent modification of the centimeter grid method for pelvic inlet plevimetry may be described in its essentials as follows:

1. The patient is placed on the roentgenographic table in a semirecumbent position which is maintained by a back rest. In placing the patient in position we endeavor to make the pelvic inlet horizontal.

2. The level of the pelvic inlet above the sensitive film is established as follows: (a) By means of calipers the vertical distance is measured from some point on the table top to a point on the anterior surface of the symphysis pubis 1 cm. below its superior border. (b) By means of calipers the distance is determined from the interspinous space between the fourth and fifth lumbar vertebras, as determined by palpation, to the table top. For practical purposes, an imaginary line drawn between the

posterior point on the body and the point on the upper and anterior surface of the symphysis will bisect the plane of the pelvic inlet. This line should be parallel to the film and this is brought about by adjusting the position of the patient so that the end points are equidistant from the table top.

3. The tube is centered in the midline about 6 cm. posterior to the upper border of the symphysis and the exposure is made.

4. The patient is removed from the table, the tube and exposed film remaining in situ.

5. The centimeter grid, a lead plate with perforations along one edge, is introduced into the same plane as that previously occupied by the pelvic inlet, as determined by the caliper readings, and a second (flash) exposure made on the edge of the previously exposed film. This is done after moving the target so that it rests directly over the perforations in the grid, still maintaining the 36 in. distance.

Comment on Inlet Technique.—In viewing the inlet film (Fig. 8) the pelvic inlet, ischial spines, and pelvic sidewalls of the outlet are readily seen. At the top edge of the film are the projected perforations of the grid representing corrected centimeters for the various levels in the pelvis. The line of corrected centimeters at the top represents the level of the pelvic inlet and this scale is used in measuring the anteroposterior, transverse, and posterior sagittal diameters of the inlet. The five rows of perforations which are seen below this level are those to be used for the 5, 6, 7, 8, and 9 cm. levels below the pelvic inlet. Thus, if we wish to measure the interspinous diameter on this film, we find the level at which they rest in the lateral film by measuring downward from the level of the pelvic inlet; if, for instance, this is 6 cm., then on the anteroposterior film we use the second or 6 cm. calibration for the determination. The same holds true for measuring the widest transverse diameter of the outlet. This level also is determined in the lateral film and the proper calibration is used on the anteroposterior film. (Note: In determining this level we use a point on the lateral film which is 1 cm. below the lower end of line [G] Fig. 6.)

THE CLASSIFICATION OF PELVIC VARIATIONS

The classification which we have used for a number of years is simple and readily comprehended. It is based upon the shape of the pelvic inlet and specifically upon the relation of the lengths of the anteroposterior and transverse diameters to each other. It is in effect a slight elaboration of Turner's original classification and is, therefore, an index to the tendencies of pelves to dolichopellism, platypellism, and the intermediate stages referred to before.

For practical purposes I do not feel that classifications based upon the subjective impressions of sex characteristics are essentially practical, especially when 10 or 12 classes may be divided into many subgroups. Furthermore, until further studies are made of male pelves in the living on a scale somewhat commensurate with those of female pelves, our knowledge of the male pelvis cannot be complete. As an instance of the importance of such further study I would call attention to the variations in male pelves which Greulich and myself found in our series.[2]

Again it should be emphasized that the anteroposterior and transverse relationships of the pelvic inlet in general are an index to these relationships throughout the pelvis in the various pelvic types. This is, of course, not true of those pelves which are grossly deformed or which have been subjected to the severe influence of disease, such as rickets.

The following pelvic variations as shown by the inlet conformation may be classified as follows:

1. *Dolichopellic or elongated type:* (Fig. 1.) The anteroposterior diameter exceeds the transverse diameter.

2. *Mesatipellic or round type:* (Fig. 2.) The anteroposterior and transverse diameters are of equal length, or the transverse diameter exceeds the anteroposterior diameter by not more than 1 cm.

3. *Brachypellic or oval type:* (Fig. 3.) The transverse diameter exceeds the anteroposterior by more than 1 cm. and less than 3 cm.

4. *Platypellic or flat type:* (Fig. 4.) The transverse diameter exceeds the anteroposterior by 3 cm. or more.

It should be understood that these are considered as basic types simply for purposes of classification, and in the description of pelves not only are these terms used, but such observations as symmetry, character of notch, of pubic arch, and of anterior segment of inlet are also added for descriptive purposes.

MATERIAL USED IN STUDY OF PELVIC TYPES

In 1939[6] the author and his associates published the results of routine roentgen pelvimetry in 800 white primiparous women. In this series the first 600 had the pelvic inlet measurements only, and in the latter 200 the entire pelvis had been measured. At the present time I am able to add 300 to the latter group in which the whole pelvis has been surveyed roentgenologically. Pelvic inlet studies are thus available in 1,100 white women.

The material upon which these studies have been made consists of patients who have been delivered in the Obstetrical Wards of The New Haven Hospital. All of the patients are of the white race and for the greater part are from American and European stock, and born in this country. The group, therefore, is probably quite representative of the mixed population which is to be found along our northeastern seaboard. This series represents cases of primiparous women who were consecutively delivered at term during a five-year period. However, in such a consecutive series it is inevitable that each year a few primigravid patients enter our wards as emergency cases advanced in labor and are delivered without previous pelvic mensuration. Such instances, however, are comparatively infrequent and consist of less than 5 per cent of the entire series. In this series, also, I have considered only term births, because it is my opinion that in any study having to do with cephalopelvic relationships, premature births should be omitted. A birth weight of 2,500 Gm. as a criterion in this connection may seem low, but this figure is that which is generally accepted as a division between premature and term infants. Obviously the great majority of our patients delivered infants whose weight was well above this figure.

DISTRIBUTION OF PELVIC TYPES

In our total series (1,100 white women), the distribution of the basic types was as follows:

Dolichopellic type occurred 205 times, or 18.6 per cent
Mesatipellic type occurred 505 times, or 45.9 per cent
Brachypellic type occurred 354 times, or 32.2 per cent
Platypellic type occurred 36 times, or 3.2 per cent

ANALYSIS OF PELVIC DIAMETERS IN 500 WHITE WOMEN

In order to obtain some idea concerning the normal range of measurements, certain data in the series of 500 women in whom the pelvis has been more completely studied may be interesting. From what has been said previously concerning pelvic variation, it is obvious that such measurements would be best studied according to pelvic type; that is the dolicho-, mesati-, and brachypellic types should be dealt with separately. The platypellic type occurs so infrequently and so often shows definite pathology that it is not considered. In this group of 500 women, the type distribution was as follows:

Dolichopellic type 113 instances or 22.6 per cent
Mesatipellic type 233 instances or 46.6 per cent
Brachypellic type 144 instances or 28.8 per cent
Platypellic type 10 instances or 2.0 per cent

The mean values for the pelvic types are shown in Table I.

As stated before, the values for pelvic height and widest outlet diameter are based on a smaller series and are shown in Table II.

TABLE I

	INLET			MIDPLANE		
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.
Dolichopellic	12.59	11.92	4.97	12.55	9.83	5.14
Mesatipellic	11.86	12.38	4.63	12.31	10.30	5.07
Brachypellic	11.07	12.81	4.34	12.14	10.48	5.08

TABLE II

	PELVIC HEIGHT (92 PELVES)	WIDEST TRANSVERSE OUTLET DIAMETER (99 PELVES)
Dolichopellic	8.8 cm.	11.3 cm.
Mesatipellic	8.8 cm.	11.9 cm.
Brachypellic	8.9 cm.	12.0 cm.

An analysis of the group reveals that some of them have dimensions which deviate considerably from the norm. It is, therefore, convenient and useful to define a range of average, in order that the measurements in any individual case may be more properly evaluated.

For clinical study, therefore, a dimension may be regarded as average if it lies within the interquartile range, which is the middle half of all pelves arranged according to the size of the dimension being studied. Any dimension outside of this range could, therefore, be spoken of as "small" or "large," as the case may be (differences of less than 0.25 cm. being disregarded). The ranges of average found in these 500 pelves are shown in Table III.

TABLE III

	DOLICHOPELLIC	MESATIPELLIC	BRACHYPELLIC
Inlet			
Anteroposterior	12.0 –13.0	11.5 –12.25	10.5 –11.5
Transverse	11.5 –12.25	12.0 –12.75	12.25–13.25
Posterior sagittal	4.5 – 5.5	4.25– 5.0	4.0 – 4.5
Midplane			
Anteroposterior	12.0 –13.0	11.75–13.0	11.5 –12.75
Transverse	9.25–10.25	10.0 –10.75	10.0 –11.0
Posterior sagittal	4.75– 5.5	4.5 – 5.5	4.5 – 5.5

If we wish to consider the pelvis as a whole in reference to its being small, average or large, it is my opinion that the anteroposterior diameter of the inlet may be used as a criterion for such classification since it appears to be the most important single dimension. Using this diameter as a yardstick, therefore, it appears that we may designate "small" pelves in the various types as follows:

Dolichopellic type A. P. Diam. less than 12.0 cm.
Mesatipellic type A. P. Diam. less than 11.5 cm.
Brachypellic type A. P. Diam. less than 10.5 cm.

OPERATIVE INTERVENTION IN 500 WHITE WOMEN

In considering operative intervention per se in its relation to pelvic conformation in the series (500 pelves) a truer picture of the situation is seen if we omit the consideration of low or outlet forceps. The reason for this is that in the primiparous woman the indications for this usually simple procedure are too broad for simple analysis. Breech extraction, because of breech presentation is also not considered.

In this group of 500 white patients, labor was terminated by operative intervention according to the above definition 33 times or in 6.6 per cent of cases. It is interesting to group such procedures according to pelvic type as follows:

Dolichopellic Group: 113 pelves, 6 operations or 5.3 per cent of 113 labors.

Mesatipellic Group: 233 pelves, 8 operations, or 3.4 per cent of 233 labors.

Brachypellic Group: 144 pelves, 19 operations or 13.2 per cent of 144 labors.

Platypellic Group: 10 pelves, 1 operation or 10.0 per cent of 10 labors.

If we separate these operations into those which were done chiefly or solely because of the presence of abnormal pelvic conformation, we find the following:

Dolichopellic type, 113 cases, 3 operations or 2.6 per cent.
Mesatipellic type, 233 cases, 1 operation or 0.4 per cent.
Brachypellic type, 144 cases, 11 operations or 7.6 per cent.
Platypellic type, 10 cases, 1 operation or 10 per cent.

These latter figures re-emphasize a previous statement that the most favorable type of pelvis for successful childbearing is one whose inlet is essentially round (mesatipellic) and not the transversely oval pelvis (brachypellic or platypellic).

LOW FORCEPS

As stated before, the indications for low forceps are in general so broad that analysis is not likely to be very significant. Nevertheless, the figures are interesting and may show trend. The occurrence was as follows in the 500 cases:

Dolichopellic type	113 pelves	low forceps 27 times	or 23.8%
Mesatipellic type	233 pelves	low forceps 48 times	or 20.6%
Brachypellic type	144 pelves	low forceps 23 times	or 15.9%

In commenting upon this frequency of operation, it may be said that if the indications for low forceps were based upon pelvic conformation alone, this is what might be expected; that is, in the dolichopellic type with relatively convergent pelvic sidewalls and therefore relative transverse narrowing of outlet, the incidence of low forceps might be expected to be higher than in the brachypellic type where broadening of the outlet is a significant feature. Obviously, the incidence in the mesatipellic type would occupy a midposition. The figures show the incidence of low forceps to be one-third greater in the dolichopellic type than in the brachypellic.

FETAL AND MATERNAL MORTALITY IN THE SERIES OF 1,100 PRIMIPAROUS WHITE WOMEN DELIVERED AT TERM

In this series of 1,100 women there were no maternal deaths and 17 fetal deaths. Among the latter, there were 3 cases showing gross fetal abnormalities and three cases of ante-partum death resulting in the birth of a macerated fetus.

CONCERNING THE ETIOLOGY OF PELVIC VARIATIONS

In the consideration of these variations in pelvic architecture it is interesting to speculate concerning the etiologic factors which may be concerned in their production. The greatest changes from the fetal to the adult type of pelvic architecture occur at or near the time of puberty. This has been shown in the studies of Greulich and myself,[7] who have observed these changes in a single group of individuals by roentgenologic study over a period of years. The recent studies of the pelvis in male and female children by Morton and Hayden[8] also substantiate this opinion. A part of their summary follows: "These findings suggest that both males and females start out life with pelves which are identical in type and that the major differences observed in adult male and female pelves do not appear until puberty and are, therefore, due to the influence of the sex hormones." However, these authors also suggest that other factors than sex, such as nutrition and disease, probably play major roles. Some years ago I suggested that nutrition may play such a major role and stated the following: "The predominant type of pelvis which was formerly seen in clinics may have actually changed in character within a generation. When one considers alteration in environment surrounding female infants and adolescent children during the past twenty-five years, changes brought about not only by a great difference in diet, but by such influences as outdoor life and life in the open, it must be admitted that the environment for this group has

changed indeed during that period. When one further considers the sedentary habits, the type of clothing, the diet, and general restrictions that previously were a part of the life of female infants and children, may one not speculate as to the effect of such an environment on the adult form of the female pelvis. That changes in environment can effect skeletal changes in a large population is witnessed in recent years by the extraordinary lessening of the incidence in children of severe rachitis.''[9] In surveying the results of Greulich and myself in studies in women of the college group, as contrasted with those of the clinic group, it would appear that environment during the growth period was a factor in the lessening of the number of the brachy- and platypellic types of pelves found in the former group.

For purposes of emphasis I repeat a portion of one of our tabulations here:

	104 STUDENT NURSES	582 CLINIC WOMEN
Dolichopellic	37.5%	15.0%
Mesatipellic	44.2%	44.8%
Brachypellic	18.2%	34.3%
Platypellic	–	5.6%

It seems probable that, as far as variations of the pelvis are concerned, both nutritional and hormonal influences play major roles, and it may indeed be that one of the effects of increased hormonal activity at the time of puberty is to preserve the general fetal conformation (dolichopellism). The evidence for this statement is not overwhelming, but there is some evidence for its consideration.

In a recent study in mental and physical growth in pubertas precox made by Gesell, Thoms, Hartman, and Thompson,[10] the findings in a girl who had been under observation for fifteen years formed the basis of the report. The child at the age of three and one-half years underwent all the phenomena of puberty including menstruation. In this instance, therefore, the hormonal influence may be said to have been abnormal, an influence extending over a relatively long period of years and which, therefore, might give some suggestion of its influence on the formation of the adult pelvis. The findings at the age of seventeen are of considerable interest. At that time she presented a typical dolichopellic type pelvis; anteroposterior diameter of inlet 12.0 cm., transverse 11.25 cm., all of the other diameters and contours of the pelvis corresponded to what we consider as the typical elongated or dolichopellic type.

Other evidence that the sex hormones may have a definite influence on bone formation is found in the interesting report of Hills and Weinberg[11] on the influence of estrin on callous formation. They report three cases of fracture with delayed union which were treated with estrogenic hormone with resultant signs of increased callous formation. Interesting also are the findings of Pfeiffer and Gardner,[12] who found that in pigeons the administration of estrogenic substances during ovulation produced an increased density of bone.

From such evidence as the above it may be permissible to conjecture that the incidence of the increased secretion of sex hormone at puberty

expresses itself in one of its functions by tending to prevent undue softness of bone, which in itself may result from certain mineral imbalance occurring during the early puberal epoch, a period of relatively rapid skeletal growth.

ROENTGEN PELVIMETRY AS A ROUTINE PROCEDURE

After a period of nearly six years in which all primigravid women in our prenatal clinic have had roentgen pelvimetry, it might be well to consider such a routine in the light of its value as a clinical procedure. I think most observers will agree at the present time that external pelvimetry is of but little use in determining actual pelvic capacity, and for a comparative study by the author on this subject, reference is here given.[13] It seems clear that if pelvimetry is a valuable procedure at all, we must have accurate observations. In the living woman it is impossible to secure such data except by means of roentgen techniques.

It is, of course, evident that most women have pelves which are adequate for the delivery of most babies, but scientific obstetrics cannot be conducted on any such philosophy, for applied to the individual case it is obviously fraught with danger. Most obstetricians of experience will recall instances where an unsuspected midplane contraction or other pelvic abnormality was responsible for an unlooked for difficult forceps operation, often accompanied with the loss of the baby. The routine use of antenatal roentgen pelvimetry should and does anticipate many of such difficulties. Not infrequently I have seen patients who from all other evidence seem to possess adequate pelves and yet have found upon roentgen examination some restriction of capacity in one or more of the important pelvic planes. This does not mean that such patients were treated radically, but it does mean that in many instances treatment was modified to suit a situation which was well understood.

It does not appear that routine roentgen studies tend to radicalism in obstetric procedure. Our figures for major obstetric operations in these 1,100 primiparas are as follows:

Cesarean section	26 times, or 2.3%
Version and extraction	5 times, or 0.4%
Midforceps	39 times, or 3.5%

Furthermore, it is obvious that some of these operations were done for other than difficulties associated with pelvic conformation.

In discussing the routine use of these roentgenographic procedures, it should be re-emphasized that the use of two views on flat films as described is not only entirely adequate for such a pelvimetric survey, but also renders the cost of the procedure well within the limits of most of the usual laboratory techniques. On our ward service in which teaching is carried out, the films of each primigravida are made available as soon as the patient enters the hospital for delivery. At this time the morphologic aspects of the pelvis are again reviewed by those attendant upon the delivery. In addition, the prenatal record is consulted concerning the pelvic dimensions. An observation concerning routine pelvimetry which has been of interest to me is the fact of its reception and adaptation to private practice by many of the obstetricians practicing

in my community. It is their feeling, as well as that of the members of our staff, that such a roentgen survey of the pelvis in the primigravid woman offers many distinct advantages and no disadvantages. Furthermore, this group have found these flat films of ready interpretation and have not of necessity had recourse to the opinion of the roentgenologist, or of one specially skilled in film interpretation. In this connection it should be emphasized that this bears out what the author has stated on previous occasions; namely, that the roentgenologist should not be expected to furnish opinion regarding prognosis in the clinical problems of a field where his experience obviously may be limited.

In discussing the routine use of roentgen pelvimetry in the primigravid patient, we should mention its great value in patients with borderline pelves and in the primigravid woman with a breech presentation. In the latter situation it seems quite clear that in most instances one who attempts to deliver such a presentation without a knowledge of pelvic conformation and certain pelvic dimensions is not practicing modern scientific obstetrics. With regard to the borderline pelvis, not only is the information with regard to pelvic capacity useful, but views taken during labor may be of signal value in noting the progress of the labor. Mention should also be made of the value of roentgen studies in estimating fetal size and maturity, and reference to the author's work in that field is here given.[14-16]

In conclusion, it is interesting to recall these words of wisdom written in 1886 by an American physician, Dr. Henry Morris,[17] "It has been said that since the world began no two women have had pelves which exactly resembled each other in every particular; that in each case there has been some difference more or less minute, by which any pelvis can be distinguished from all others. While this is probably an exaggeration, it is nevertheless true that the female pelvis is subject to many variations, both as regards its size and its shape. The 'normal pelvis,' therefore, is more of an ideal than of a reality—a pelvis conceived from the 'good points' of many pelves, whose diameters are arrived at from averages derived from the measurements of thousands of specimens."

I wish to express my appreciation of the interest and assistance in these studies of Dr. Hugh M. Wilson and his associates of the Department of Roentgenology, Yale University. I am also deeply grateful to Dr. Irving Friedman for assistance in the preparation of certain statistical material.

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EXTRACELLULAR WATER IN LATE PREGNANCY AND ITS RELATION TO THE DEVELOPMENT OF TOXEMIA

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MANY writers have regarded excessive or rapid weight gain in late pregnancy as a premonitory sign of impending toxemia, and have established that the incidence of toxemia is increased in those women who gain too much or too rapidly. Such weight gains do not always precede toxemia, and not all women gaining excessively do develop toxemia. In many of those women who do become toxic, part of the excessive or rapid weight gain presumably represents the accumulation of edema water. Others may add fat or protoplasm. It would be interesting to separate the water-gainers from the protoplasm-gainers, and to compare the incidence of toxemia in the two groups. Possibly such a separation might have a practical value in the detection of developing toxemia.

In the present study we have attempted a differentiation between women accumulating water and those gaining protoplasm, by measuring the "available water" for thiocyanate distribution. This measurement is thought to give an approximation to the extracellular water of the body. We realize that the water gained in pregnancy and in toxemia may not be wholly extracellular.

The principle of the test is simple. Equation of "available" water with extracellular water depends upon 2 assumptions, neither of which is wholly valid. The assumptions are: (1) injected or ingested thiocyanate does not enter cells of the body, and (2) the thiocyanate attains the same concentration in all body water outside of the cells, so that the plasma concentration is the same as that in the interstitial fluids. As for the first assumption, thiocyanate does enter the red blood cells (Crandall and Anderson[1]), though these corpuscles are not typical cells; thiocyanate may also enter the salivary glands and pancreas. In the second place, there is usually a difference of about 10 per cent in the concentrations of thiocyanate in plasma and in edema fluid (Lavietes, Bourdillon and Klinghoffer[2]).

The procedure is: (1) inject an accurately known amount of thiocyanate, (2) allow a period of several hours for a uniform distribution of the salt, (3) measure the urinary loss of thiocyanate during the equilibration period, (4) determine the plasma (or serum) concentration of thiocyanate after equilibration, and (5) calculate the volume of "available" water by dividing the plasma concentration into the quantity of thiocyanate remaining in the body.

MATERIAL

We selected from the ante-partum clinic 180 patients who manifested no signs or symptoms of toxemia, other than excessive weight gain in some cases. These women were in their last six weeks of pregnancy. Each patient was given intravenously 20 ml. of 5 per cent sodium thiocyanate (Abbott's sulfocyanate), and asked to come back the following day bringing with her all urine passed in the interim. Thus there was a period of eighteen to twenty-four hours (usually twenty-one hours) for the thiocyanate equilibration. When the patient returned, a blood sample was taken, and the urine collection was completed.

Thiocyanate was determined in modified Folin-Wu filtrates of serum and urine. The Evelyn photoelectric colorimeter was used for the measurement of the color developed by the addition of an acid solution of ferric nitrate. The method has been described elsewhere (Chesley[3]).

The completeness of the urine collections was checked by determination of the creatinine excretion. In the few cases in which large volumes of urine had obviously been lost, the test was not recorded.

The "available" water was calculated in terms of percentage of the body weight. Surface area calculations were not made, because it was thought that the usual formulas do not obtain in late pregnancy.

In many patients the measurement of available water was repeated on the third to ninth (usually sixth) day after delivery. When the test was repeated, a "blank" blood sample was first taken, in order to correct for any residual thiocyanate from the first test. The thiocyanate was then given by mouth, and twenty hours were allowed for equilibration.

RESULTS AND DISCUSSION

Normal Pregnancy.—Toward the end of normal pregnancy the proportion of available water to body weight varies greatly, the proportion depending chiefly upon the body weight. In women weighing more than 200 pounds, the normal proportion of available water is about the same as that usually alleged for nonpregnant women, i.e., 20 to 26 per cent. But in women weighing less than 120 pounds the normal proportion of available water is much higher, 33 to as much as 37 per cent of the subject's weight. If we accept without reinterpretation the published data for nonpregnant women, normal pregnancy would seem to double the available water in light-weight women without adding much to the heavy-weight patients. This does not seem reasonable, and a reinterpretation of published data for nonpregnant individuals will be offered presently.

All data for pregnant women are represented in Fig. 1. The lines were drawn arbitrarily in an effort to define the normal proportion of available water in relation to body weight. If we exclude the patients who developed hypertensive toxemia subsequent to the measurement, the upper line includes over 85 per cent of all cases. The normal limits are represented as curves for three reasons: (1) such curves seem, by inspection, to fit the general trend of the points, (2) most of the pretoxemic patients are thus relegated to the "abnormal" area, and (3) the patients thus separated as "abnormal" lose much larger quantities of available water after delivery. Whether these are valid and acceptable criteria remains to be seen. In the present series of 180 cases such arbitrary delimitation of the normal range of available fluid seems to be justi-

fied. Further study, now in progress, will perhaps give a more definite answer. (Incidentally, the curves were tentatively drawn by the first criterion before the outcomes of the pregnancies were known.) Whatever the form of the curve, the data clearly demonstrate a marked difference between light-weight and heavy-weight patients, which must be considered in any interpretation of measurements of the available water in pregnancy.

The only publication in which there is any suggestion that the proportion of available water to body weight may vary with the weight, in nonpregnant individuals, is that of Brodie, Brand, and Leshin[4] who

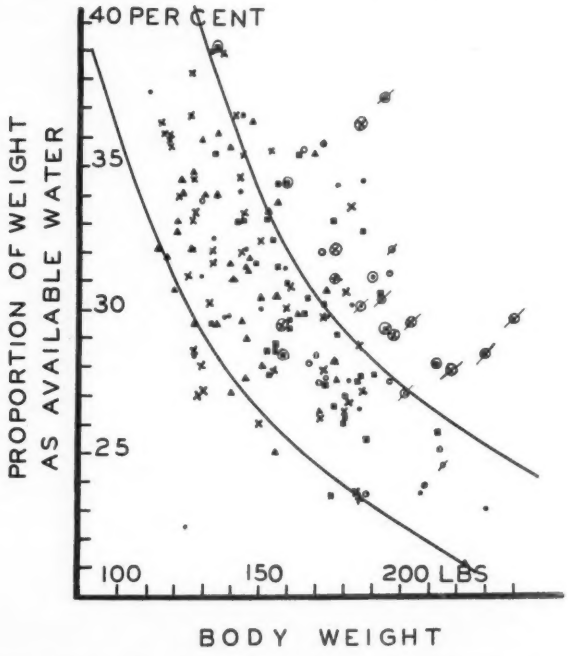

Fig. 1.—The relation between body weight and the proportion of the weight represented by available water. All cases are shown. The weight gains in pregnancy are denoted as follows: Less than 10 pounds ●; 11 to 20 pounds ×; 21 to 30 pounds ▲; 31 to 40 pounds □; 41 to 50 pounds ○; more than 51 pounds ϕ. Circled symbols indicate patients developing toxemia of pregnancy subsequent to the measurement of available water. Circled symbol with cross-stroke indicates borderline toxemia as described in text. Further work indicates that the descending limbs of the curves perhaps are too steep and that no patient should show available water amounting to more than about 37 per cent of the body weight.

report on 6 cases. In other papers, few cases have been studied and most of the body weights have been nearly average. Crandall and Anderson[1] measured the available water in 3 nonpregnant women, and Stewart and Rourke[5] have recently recorded data for 19 normal women. These data have been re-calculated and plotted in Fig. 2, in the same manner as the data for pregnant women were plotted in Fig. 1. While it is hazardous to draw curves for these few points, there does appear to be some correlation between the body weight and the proportion of available water; this correlation appears grossly to be similar to that plotted for pregnant women.

If curves approaching the form of those drawn in Fig. 2 actually do describe the relation between body weight and the proportion of available water, then the data in Fig. 1, for pregnant women, become more comprehensible. We need no longer consider that pregnancy doubles the available water of the 100-pound woman and adds no water in the 200-pound subject, but rather that pregnancy merely shifts upward the curve for all pregnant women.

(The data of Stewart and Rourke[5] fall considerably below the volumes found by other investigators. The reason for this is very probably the fact that Stewart and Rourke[5] base their calculations upon the serum thiocyanate concentrations as determined at thirty to forty minutes after

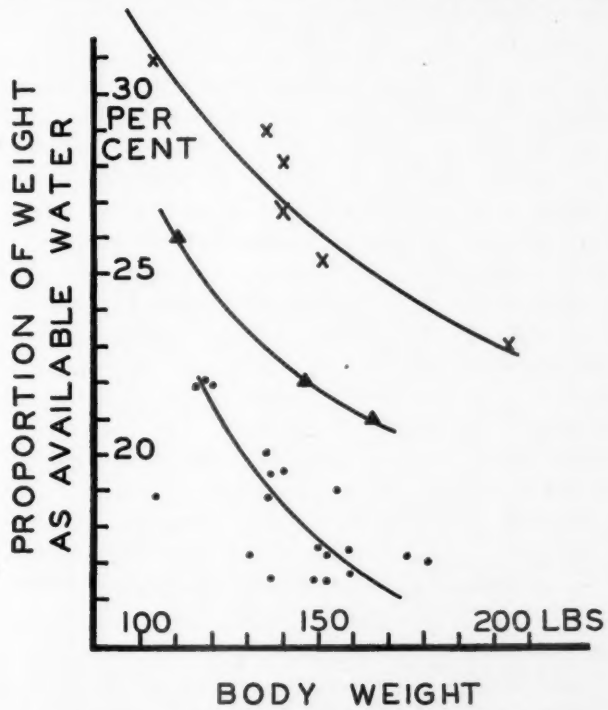

Fig. 2.—Published data of other writers, for available water in nonpregnant adults. Data of Brodie, Brand and Leshin (×) for men, using bromide method. Data of Crandall and Anderson (▲) and of Stewart and Rourke (●) for women, using thiocyanate method.

the injection of the thiocyanate. It has been shown by Goudsmit, Louis, and Scott,[6] and by Gilligan and Altschule[7] that the calculated volume of available water is considerably lower at this time than are the volumes calculated from serum concentrations determined some hours later. Perhaps the thiocyanate does not become distributed uniformly in extracellular water within half an hour, and the calculated volume of available water is too low. Or perhaps with longer equilibration periods some thiocyanate enters certain cells or is bound in some manner, thus giving falsely high values for the available water. The latter possibility would seem improbable from observations made by several writers: the calcu-

lations of available water, in nonpregnant individuals, from the serum concentrations of thiocyanate at four, eight, and twenty-four hours after injection of thiocyanate are in close agreement, which at least rules out the *progressive* binding or intracellular loss of thiocyanate.)

In pregnancy, even the twenty-one-hour period which we have allowed is not sufficient for an even distribution of thiocyanate if we consider the amniotic fluid as extracellular water. For at the end of twenty-one hours the concentration of thiocyanate in amniotic fluid is only about one-half that in serum. After thirty-six hours the concentration in amniotic fluid is still but two-thirds of that in serum. Our measurements of available water, then, include about half of the amniotic fluid. Presumably it also includes the extracellular water of the fetus.

Pretoxic Patients.—When the measurements of available water were made, no patient manifested hypertension, proteinuria, or any other sign of toxemia of pregnancy, except possibly abnormal weight gain in some cases. Clinically the pretoxic patients could not be separated from those who were to complete their pregnancies without toxemia.

As Fig. 1 shows, most of the patients who did become toxic had already gained excess available water at the time of the test. However two (possibly three) cases of toxemia did appear among those patients having normal proportions of available water at the time of the test. In one of these women, the determination of available water was made six weeks before the first elevation in blood pressure; possibly she had accumulated water in the interim. The second patient showed mild elevations of the blood pressure within a week of the time at which we found a normal proportion of available water, and therefore the conventional signs of toxemia apparently were not preceded by extracellular water retention. A third patient coming within the normal area showed a mild hypertension first appearing on the third day post partum; no other signs or symptoms of toxemia were manifest.

If we divide all patients into two groups, the one comprising patients with normal proportions of available water and the other those with excessive water, we find a remarkable difference in the incidence of toxemia. Among 141 patients with normal proportions of available water, 2 (or 3) developed hypertensive toxemia (mild pre-eclampsia), an incidence of 1.42 (or 2.13) per cent. In the 39 patients having excessive water, 9 became unquestionably toxic, and an additional 7 showed borderline blood pressures (near 140/90) before or after delivery. Four of these patients had only a post-partum hypertension. Thus the incidence of pre-eclampsia with hypertension is at least 23.1 per cent. If the borderline cases all be included, and certainly they were not strictly normal, the incidence of toxemia would be 41.0 per cent.

In brief, it would seem that a high proportion of pre-eclamptic patients accumulate extracellular water in abnormal amounts before hypertension, proteinuria, or (often) excessive weight gain becomes evident. Not all patients showing such abnormal water retention, however, will later develop the signs and symptoms of pre-eclampsia. Since most of

the patients in this group were put on a diet restricting salt, water, and calories, it is conceivable that the development of pre-eclampsia was modified or even aborted.

Toxemia of pregnancy remains essentially undefined. We are learning more and more of its signs and symptoms, and by routinely taking blood pressures in pregnant women, we are today diagnosing toxemia in patients who would otherwise, and in another time, have been considered normal. Hypertension is not universally present in toxemia, nor is its presence a sine qua non for the diagnosis of toxemia. This might be emphasized by citation of statistics on eclampsia. In a series of 215 eclamptic patients, the systolic blood pressure was consistently less than 150 mm. Hg in 84, or 39 per cent of all cases. In about 12 per cent the systolic pressure was less than 140 mm. Hg whenever measured. Hypertension is merely a sign, and possibly a late sign, of some fundamental disturbance, the nature of which is unknown. Perhaps water retention is an earlier and even a more general sign of the disturbance which we call toxemia.

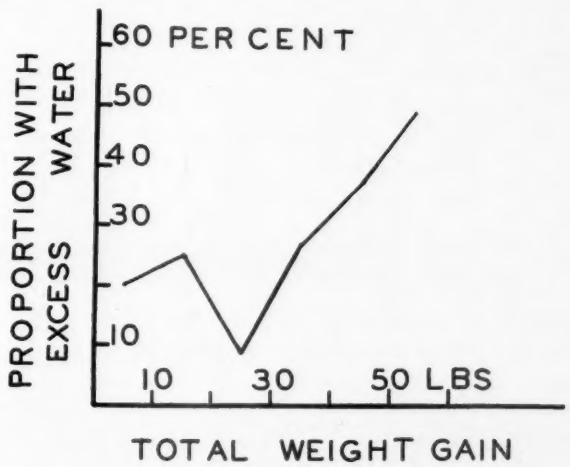

Fig. 3.—The relation between excessive weight gain and excessive water gain in late pregnancy. Most patients with excessive weights gains do not have excessive available water, and do not develop toxemia.

RELATION OF WEIGHT GAIN TO EXTRACELLULAR WATER

It is a common clinical practice to weigh the pregnant patient regularly, because edema formation may often be revealed by the excessive or rapid weight gain. It is interesting, therefore, to compare the weight gain with the measurements of extracellular water. Reference to Fig. 3 will show that there is some correlation between the total weight gain and the proportion of available water. Yet in the 2 patients gaining more than 60 pounds, the proportions of available water were perfectly normal, indicating that these women had gained protoplasm. On the other hand, half of the women having too much available water had had normal total weight gains (less than 20 pounds). A consideration

of the data leads to the conclusion that the available water measurements are more reliable than total weight gain in picking out potential toxemia patients.

When we consider rapid weight gains, we again find that many pre-toxemic patients do not show any abnormality. In the first place, rapid weight gain is very frequently absent in developing toxemia. For instance, in a series of 236 pre-eclamptic cases occurring in 1935 and 1936, rapid weight gain (more than 1½ pounds per week) preceded hypertension in only 22.9 per cent of cases. (No account has been taken of rapid weight gain after the appearance of hypertension.) Second, the majority of patients with excessive available fluid had not shown rapid weight gain at the time of the test.

LOSS OF AVAILABLE WATER IN DELIVERY AND EARLY PUERPERIUM

We have not made a systematic study of the extracellular water just before and just after delivery, but in 52 cases the measurement of available water was repeated post partum. The original determination was made anywhere from one day to as much as five weeks before delivery,

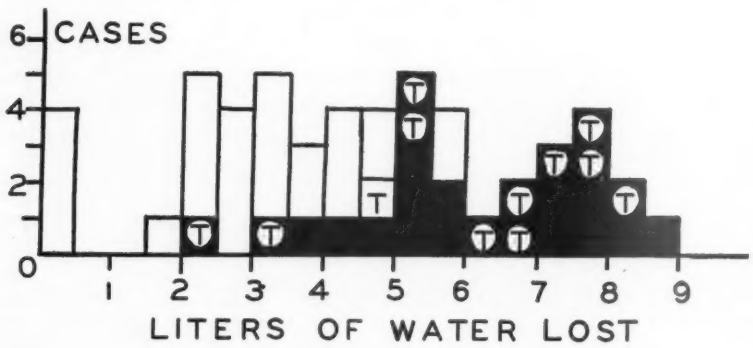

Fig. 4.—The loss of available water from the time of the ante-partum measurement until the sixth day (average) post partum. Patients grouped in the normal area of Fig. 1. □ Patients grouped in abnormal area of Fig. 1, denoting excessive available water ■. Patients developing toxemia are indicated by T.

while the repetition was usually made on the fourth to sixth day post-partum. Thus many of the patients gained or lost unknown volumes of extracellular water between measurements, and the data have little quantitative value.

These measurements of available water, made post partum, do have some value, in that they demonstrate that those patients coming within the "abnormal" area in Fig. 1 are the individuals who lose the most water between the times of the first determination and the post-partum repetition of the test. In Fig. 4 we have plotted the frequency distribution of these water losses, and indicated which patients had come within the abnormal area, and which ones developed pre-eclampsia. Of the 39 patients who had excessive available water at the time of the antepartum test, 25 had rechecks; 80 per cent of these lost unusually large amounts of available water between tests.

SUMMARY AND CONCLUSIONS

We have measured the body water available for thiocyanate distribution (extracellular water) in 180 normal women in the last six weeks of pregnancy.

A curvilinear relationship is found between the body weight and the proportion of body weight represented by available water. On the basis of the few published data, it is suggested that a similar relationship exists in nonpregnant women.

Patients who are found to have excessive available water, although apparently normal otherwise, are prone to develop the classical signs and symptoms of pre-eclampsia. Pre-eclampsia very seldom appears in those patients having normal proportions of available water in late pregnancy.

Measurement of available water affords a more reliable index to the danger of developing toxemia than does weight taking.

Patients who have excessive extracellular water in pregnancy will have lost large amounts of this water by the sixth post-partum day.

We wish to take this opportunity to thank Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters for reading and criticizing the typescript.

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HISTOLOGIC CHANGES IN THE OVARY FOLLOWING GONADOTROPIN ADMINISTRATION*

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INTRODUCTION

THE interrelationship of the anterior pituitary and the gonads was first demonstrated by Zondek and Aschheim,[1] Smith and Engle[2] in 1927. The utter dependency of the gonads on the anterior pituitary is readily appreciated. Less understood, however, is the controlling influence exerted by the gonads on the hypophysis. On first thought it might seem that the main concern of the anterior pituitary-gonad relationship is the maturation of the Graafian follicle, the expulsion of the egg, and the formation of the corpus luteum. Such a conception fails to take into account the component parts of the ovary that are subject to stimulation and play a role in the anterior pituitary-gonad complex.

*Aided, in part, by a grant from the Scientific Committee of the American Medical Association.

The component parts of the ovary, aside from the ovum are:

1. The granulosa cells
2. The theca interna
3. The stroma of the ovary
4. The vascular bed
5. The corpus atreticum

Stimulation of the ovary by the anterior pituitary will depend on the quality, quantity, and admixture of the various gonadotropic factors of the hypophysis as well as the sensitivity and receptiveness of the various components of the ovary. Any disturbance in this intricate and delicate mechanism may cause an imbalance with consequent sequelae that will effect not only the anterior pituitary-gonad balance but also distant organs as the uterus, endometrium, genital tract, and breasts that depend on balanced sterol production.

It has been well established that the ovaries of experimental animals react in different ways to the various gonadotropic factors.

For instance, Engle[3] has shown that the immature mouse ovary responds to extracts of pregnancy urine by exhibiting follicle atresia, luteinized follicles, and no ovulation, but responds to extracts of the anterior pituitary by follicle stimulation and ovulation. In the human being, the consensus has been that anterior pituitary-like substances fail to stimulate the ovary to produce follicle maturation, ovulation, and corpus luteum formation (Geist,[4] Hamblen and Ross[5]). The recent work of Davis and Koff,[6] and Siegler and Fein[7] tends to show that such stimulation may be obtained by the use of pregnant mares' serum. In previous communications, we have maintained that neither anterior pituitary extracts, nor equine, nor chorionic gonadotropins were capable of producing orderly maturation of follicles, ovulation, and corpus luteum formation in patients with nonreceptive or subnormal ovaries (primary ovarian insufficiency). However, in patients with normal ovaries, the normal processes may be augmented or even duplicated.[8, 9] Hartman[10] has shown that in the rhesus monkey, though ovulation could be induced, there was no guarantee that an endocrine condition favorable to the implantation of a fertilized ovum existed.

The purpose of this communication is to point out that the various gonadotropins undeniably are capable of stimulating the human ovary. What is the nature of this stimulation as seen histologically in the normal and subnormal ovary? Though ovulation cannot be induced in certain subnormal ovaries, nevertheless certain components of the ovary are responsive which may account for the clinical improvement seen in certain cases of oligomenorrhea, amenorrhea, menorrhagia, dysmenorrhea, etc.

HISTOLOGIC CONSIDERATIONS

A. *Ovarian Stroma.*—The stroma of the ovary is as much a gland of internal secretion as is the follicular apparatus. In various experimental animals the part played by the stroma cells is more clearly defined. The stroma may be influenced directly by the anterior pituitary or by its contiguity to active granulosa cells. The latter fact is clearly brought to point in the examination of granulosa cell tumors.

The connective tissue surrounding focal masses of granulosa cells frequently shows heavy deposition of lipoids[11] (Fig. 1). In the rabbit ovary, polyhedral lipochrome cells are occasionally seen in the juxtamedullary region, particularly after small doses of gonadotropins (Fig. 2). These resemble the Leydig cells seen in the testes. Under certain conditions these stroma interstitial cells are so stimulated that all the stroma of the rabbit ovary is transformed into lipoid containing interstitum except for the granulosa cells and the surrounding thecal stroma (Fig. 3). This would tend to show that the interstitum of the rabbit ovary is not the same as the theca interna for both may respond to different stimuli although frequently responding to the same stimulus.

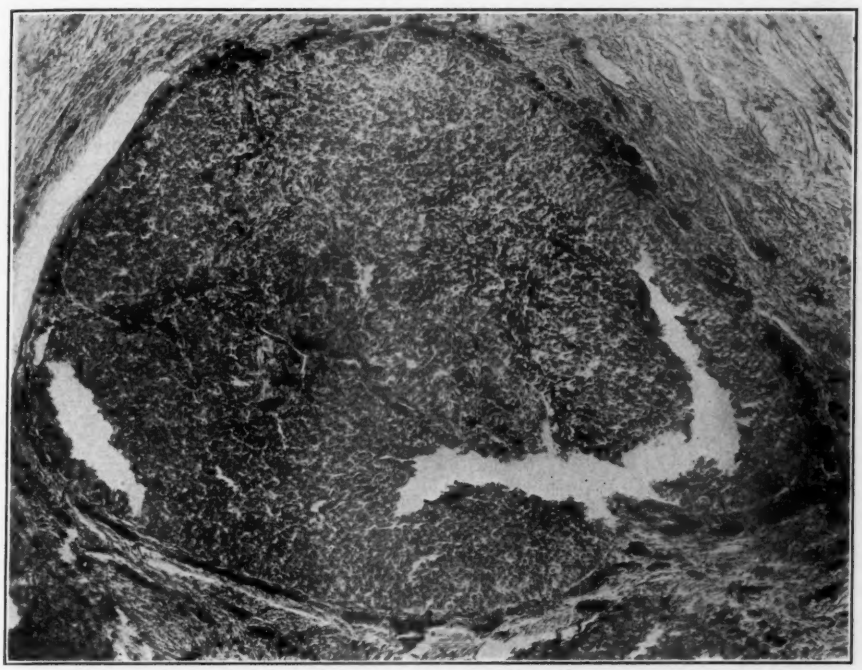

Fig. 1.—Granulosa cell tumor (mature homogeneous type). Note the periepithelial accumulation of lipoids (stained black) in the stroma simulating a thecalike reaction. (Sudan III hematoxylin-stained frozen section, ×150.) (Reprinted from Greenblatt, R. B., Greenhill, J. P., and Brown, W. R.: AM. J. OBST. & GYNEC. 37: 929, 1939.)

In the human ovary, the stroma response is not as clear-cut. Certain patches of stroma may take on a hypertrophied and vacuolated appearance (Fig. 4), and the stroma cells in certain areas become more fusiform and full with larger nuclei but the transformation is not so marked as to arrest attention. An interstitial stroma cell response, in a measure comparable to that seen in the experimental animal, may be seen in the human ovary. This occurs in the stroma about the corpus atreticum. This is seen with regularity after gonadotropin medication. Enlargement of the corpora atretica occurs with new fibroblastic activity in the core of the body, and at the periphery there is a rejuvenation of the stroma which is merely a reawakening of dormant theca interna cells (Fig. 5), which had become incorporated into the basic substance of the ovary. These appear as a palisade of polyhedral cells that resemble the Leydig cell or the paralutein cell of the mature corpus

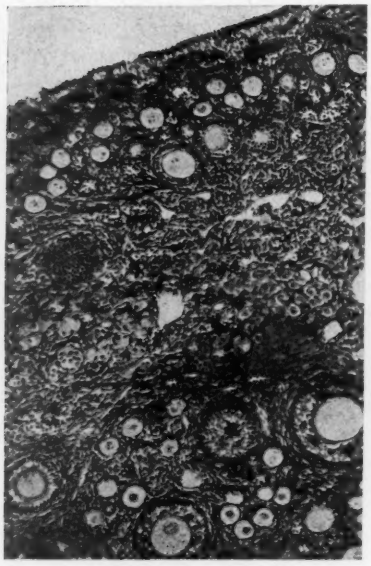

Fig. 2.

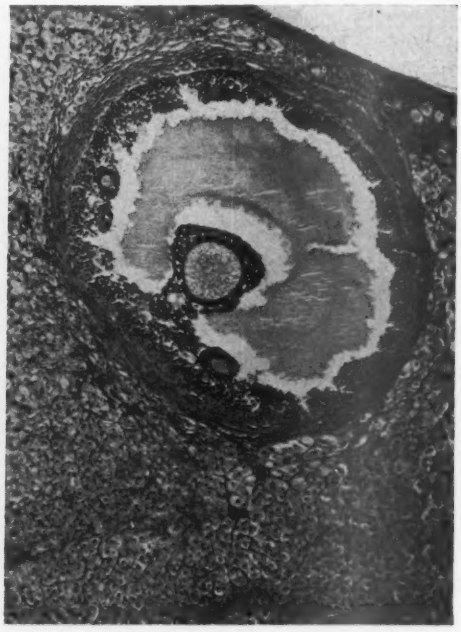

Fig. 3.

Fig. 2.—Note the polyhedral lipochrome cells in the juxtamedullary region of the ovary of a rabbit following the administration of 150 units of chorionic gonadotropin (pranturon) for three days with laparotomy on the fourth day. Note how they resemble interstitial cells of the testes.

Fig. 3.—Note that all the stroma of the rabbit ovary except the cortex, the granulosa cells of the follicle with its surrounding theca have been transformed into a lipoid containing interstitum following the administration of 1 mg. of stilbestrol (synestrol), for four days, laparotomy on fifth day.

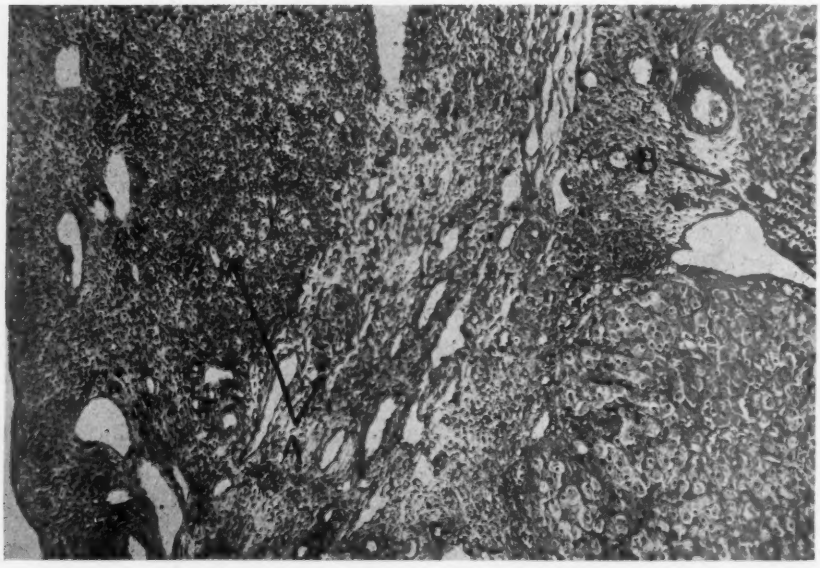

Fig. 4.—Note the patches at (*A*) of hypertrophied, vacuolated stroma cells in the cortex of the ovary. These, in a measure, resemble the paralutein cells of the corpus luteum which are visible at (*B*). Section from a human ovary following repeated doses of pregnant mares' serum for several months. (Sections by courtesy of Dr. Karl Karnaky.)

luteum. There also appears to occur a luteinization of corpora fibrosa with increased lipoid deposition in that area. Aside from this, increased vascularity of the minute vessels in the stroma are apparent, not infrequently accompanied by extravasation of red blood cells in the vicinity of corpora fibrosa as well as in the core of corpora atretica.

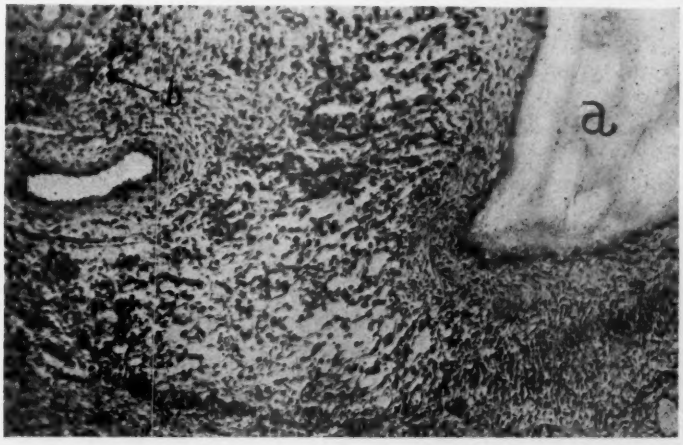

Fig. 5.—Note the palisade of polyhedral cells about the corpus atreticum (*a*). The rejuvenated stroma cells were once active cells of the theca interna which have become incorporated into the basic substance of the ovary. Note the resemblance of the theca cells to the paralutein cells of the corpus luteum at (*b*). Biopsy from human ovary following a total of 90 units of pregnant mares' serum (Gonadogen administered on the third, fourth, and fifth days of the cycle; laparotomy on the seventh day of cycle.

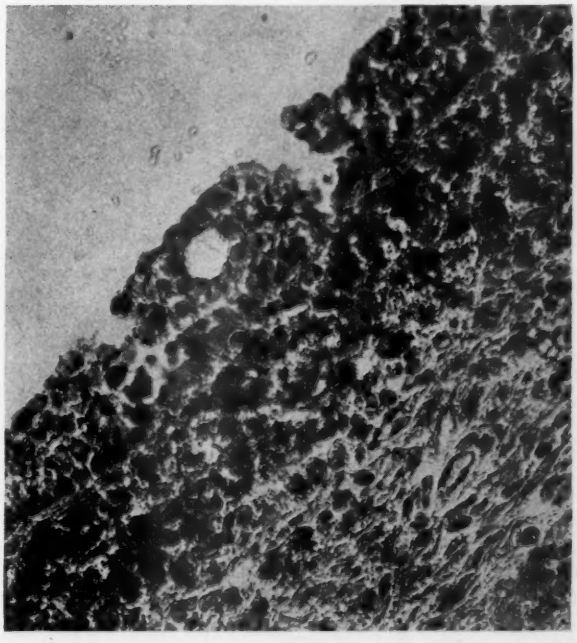

Fig. 6.—Note the luteinization of the cells of the theca interna (Sudan III hematoxylin-stained frozen section). Note the lipoid deposition (photographs black) in the theca interna, eighth day of normal cycle following the administration of anterior pituitary extract (10 c.c. of gonadotropic factor).

The luteinization of the theca interna occurs about the maturing follicle; after ovulation occurs the luteinization becomes increasingly abundant in the granulosa cells and further deposition of lipoids in the theca is arrested. If atresia of a somewhat maturing follicle occurs, then the hypertrophy and vacuolization of the theca becomes very pronounced. With impairment of the follicular apparatus by degeneration of the granulosa, compensatory theca cell hypertrophy seems to occur. Following gonadotropin medication theca cell luteinization about atretic or cystic unovulable follicles is the most constant and consistent stroma cell change (Fig. 6).

B. *The Follicular Apparatus.*—Most striking are the changes in the follicular apparatus of the ovary. Marked cystic dilatation of the follicles (distended with cloudy follicular fluid) lined by one or two seemingly compressed layers of granulosa cells showing chromatolysis and

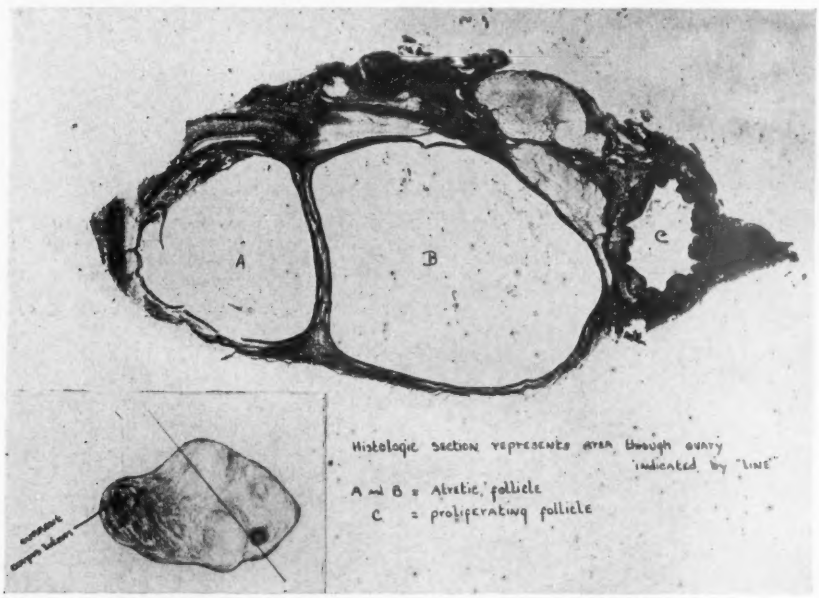

Fig. 7.—Note the atresia of the follicles at *A* and *B*. Proliferative follicle juxtaposed at *C*. Biopsy of human ovary following 90 units of pregnant mares' serum (gonadogen) administered intravenously; laparotomy fifteen hours later on sixteenth day of cycle. Note the current corpus luteum in gross drawing of the ovary.

pyknosis was the reaction most commonly present in all ovaries regardless of the type of gonadotropin medication, but most apparent after pregnant mares' serum (Fig. 7). Minimal to marked hypertrophy of the theca interna accompanied the follicular atresia. Frequently juxtaposed were follicles in various stages of maturation. Evidence of maturation of the follicle includes increase in size of the follicle, the wall lined by several layers of granulosa cells showing active proliferation as is evidenced by occasional mitotic figures, as well as signs of active secretion as is shown by the presence of Call-Exner bodies and the slight loosening of the granulosa by a coagulum giving the "streaming-out" phenomenon. The theca interna shows hypertrophy and some vacuolization of its cells as well as activity as is manifest by occasional mitoses. The perifollicular capillaries are congested (Fig. 8). Further progress in

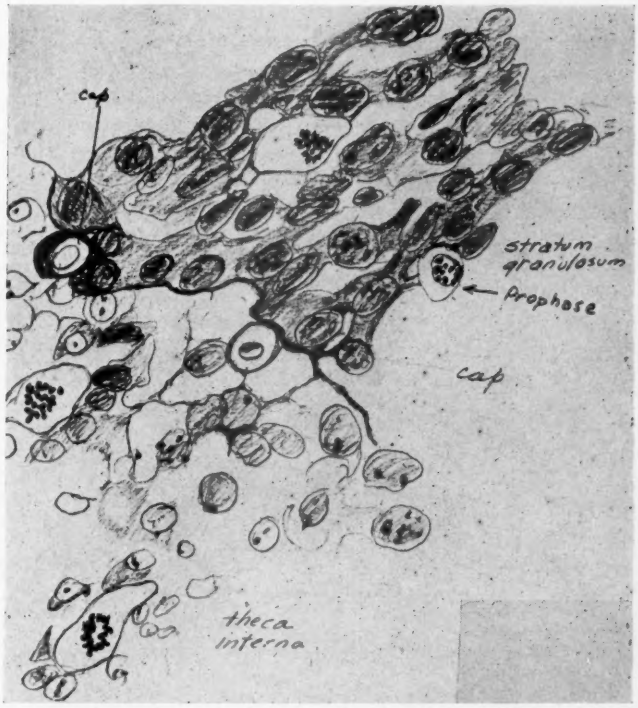

Fig. 8.—Camera lucida sketch ×1700 showing mitoses in stratum granulosa and theca interna. Biopsy of human ovary following intramuscular administration of 90 units of pregnant mares' serum (Gonadogen).

Fig. 9.—Note the pseudoluteinized granulosa cell layer (*a*), the hypertrophy of the cells of the theca interna (*b*), and the increased vascularity (*c*). Note the infolding of the membrana granulosa. Laparotomy performed on ninth day of regular cycle following administration of chorionic gonadotropin (Pranturon).

maturation is marked by the pseudoluteinized appearance of the granulosa cells (contain but the minimal amount of lipoids), marked theca cell hypertrophy with lipoid storage, increased vascularity causing the jutting inwards of the theca giving the irregular infolding appearance

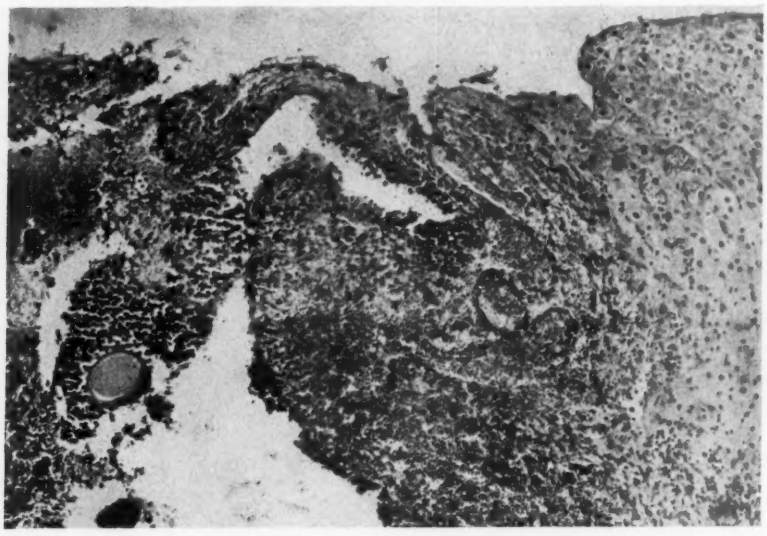

Fig. 10.—Note an apparently healthy ovum about to be washed out from the partially collapsed follicle on the ninth day of cycle following a course of equine gonadotropin. Note the dehiscence of the capsular part of the ovary, the rupture point, the basophilic coagulum, the ovum still situated in a recognizable cumulus, the decidua-like excrescence and the Call-Exner bodies in the granulosa cell layers.

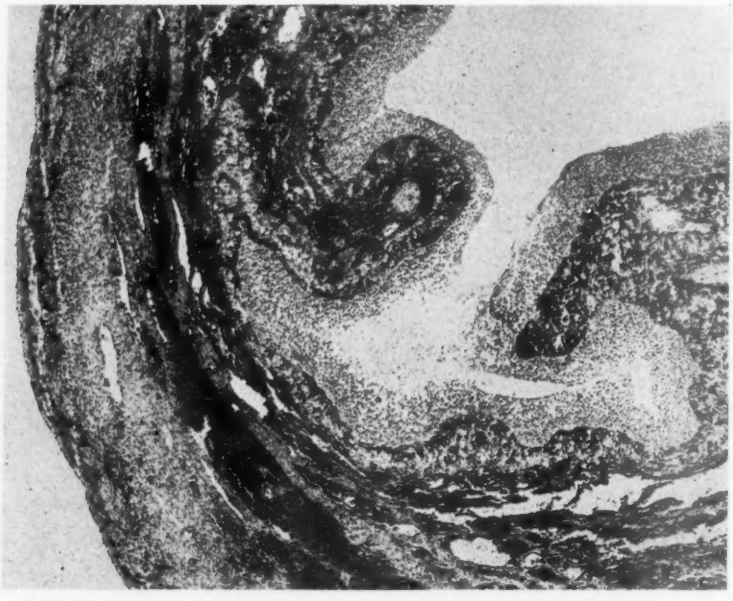

Fig. 11.—Marked congestion and perifollicular hemorrhage with disintegration of tissue following the administration of pregnant mares' serum (1,500 units of anteron). Note the pseudoluteinization of the piled-up granulosa cells and the hypertrophy of the cells of the theca interna.

to the follicle (Fig. 9). Follicle rupture with the expulsion of the ovum probably occurs just prior to this phase, but the presence of infolding of the membrana granulosa does not necessarily signify rupture of the follicle. Davis and Koff said, "No one has actually seen a follicle (human) rupture nor observed its ovum prior to its transport into

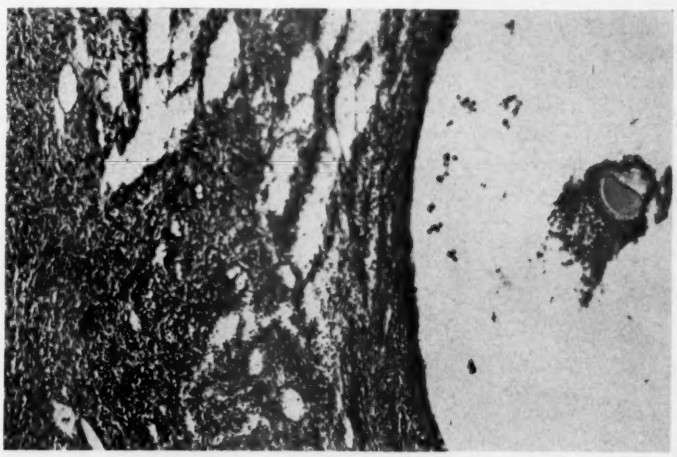

Fig. 12.—Note the follicular atresia and the degeneration of the ovum while still surrounded by its cumulus. Note the paucity of the primordial follicles in the cortex. Biopsy from a sterile patient with functional amenorrhea following the administration of pregnant mares' serum (120 units of gonadogen) intramuscularly. No evidence of corpora albicantes or corpora lutea was present in the sections examined although one abortive corpus luteum was seen.

Fig. 13.—Early corpus atreticum. Premature hyaline deposition in the thecal wall immediately beneath the membrana granulosa is noted. The imprisoned ovum surrounded by its cumulus appears normal. Biopsy of ovary followed administration of gonadotropins.

the Fallopian tube." We have been very fortunate in being able to demonstrate the process of actual rupture of the follicle in the human being. In this case it appears that rupture took place after the superficial wall, theca interna, theca externa, and surrounding stroma suffered disintegration by interstitial extravasation. Fig. 10 shows the dehiscence of the capsular part of the ovary, the partial collapse of the follicle and a normal ovum with its cumulus about to be expelled or washed out of the follicle. Note the Call-Exner bodies in granulosa cell layers of the follicle indicating active secretion. Note the mild hypertrophy of the theca interna. The only unusual or abnormal findings are the excessive extravasation of blood in the surrounding stroma and the tag of decidualike tissue; both probably due to marked response to the pregnant mares' serum which was administered.[12]

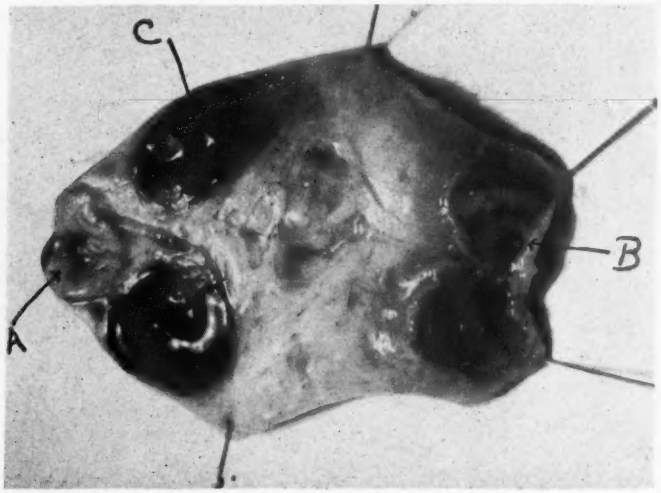

Fig. 14.—Bisected ovary showing *A*, the fully blossomed corpus luteum; *B*, fresh corpus luteum; and *C*, hemorrhagic lutein cyst, following the administration of chorionic gonadotropin with anterior pituitary synergist (10 c.c. of synapoidin) on twenty-first to twenty-third day of cycle, laparotomy on twenty-fourth day.

The orderly maturation of the follicles following the administration of gonadotropins is not frequently seen. Unpredictable is the response to a given dosage. Marked follicular stimulation, pseudoluteinization of piled up granulosa cell layers, hypertrophy of the cells of the theca interna, may be accompanied by a too vigorous response of the vascular bed component. The massive perifollicular hemorrhage and disruption of tissue is quite apparent in Fig. 11. Follicle atresia may occur because of early degeneration of the ovum (Fig. 12), disruption and desquamation of the hypertrophied granulosa cell layer. Thickening of the thecal wall with premature hyaline deposition may imprison a normal appearing ovum, thus forming the corpus atreticum (Fig. 13).

Complete shedding of the granulosa cell layer, accompanied by luteinization of the theca with hemorrhage into the cavity is not infrequently observed following gonadotropin stimulation. This is the hemorrhagic cyst which grossly may be mistaken for an hemorrhagic corpus luteum. Other forms of follicular atresia may occur due either to lack of liquor folliculi secretion or to its too rapid absorption leading to follic-

ular collapse. The occurrence of multiple corpora lutea (Fig. 14) in the same ovary following the administration of gonadotropins particularly if these are in different stages of development, may be accepted as an indication of superovulation (Fig. 15). The occurrence of a fresh corpus luteum along with a fully blossoming one is no absolute proof that the former is the result of the gonadotropic stimulant.

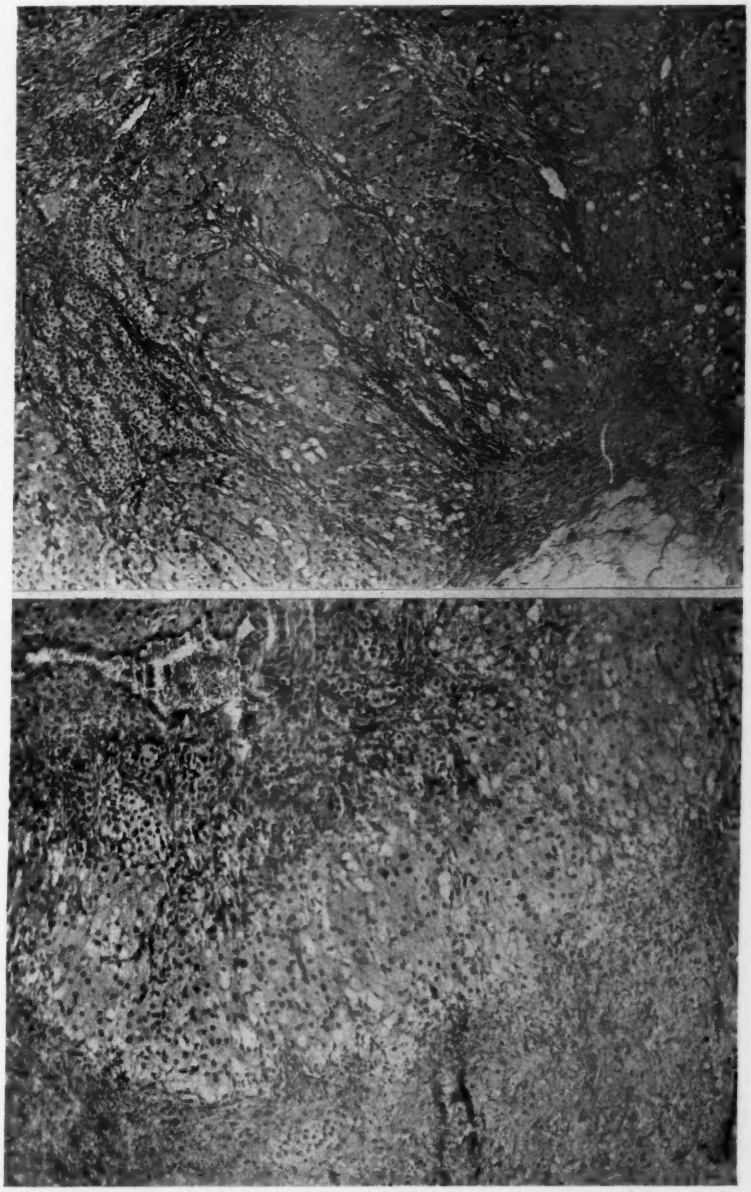

Fig. 15.—*A*, Histologic section through fully blossoming corpus luteum seen in Fig. 14 (*A*). Note the well developed fibroblastic wreath demarcating the central cavity and the mature paralutein cells growing down between the folds of lutein cells. *B*, Histologic section through the fresh corpus luteum seen in Fig. 14 (*B*). Note the ripening lutein granulosa cells and the hemorrhage into the central cavity.

Multiple corpora lutea in the same or in each of the ovaries have been observed though these are usually of the same age. Following gonadotropin medication there is frequently a rejuvenation of the degenerating cells of a previous corpus luteum. Accompanying this there is a vascular component response, i.e., fresh hemorrhage or extravasation of blood into the cavity of an older or degenerating corpus luteum (Fig. 16).

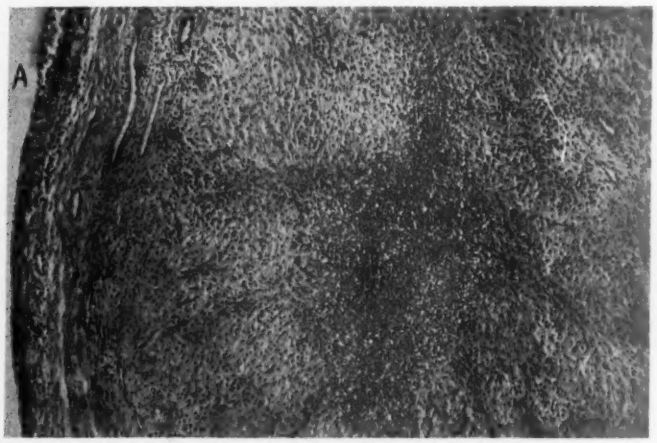

Fig. 16.—Biopsy of human ovary following pregnant mares' serum (90 units of gonadogen) intramuscularly, showing extravasation of blood into the cavity of the degenerating corpus luteum with seeming rejuvenation of the lutein cells. This corpus luteum was found deep in the cortex of the ovary. Above it at (*A*) is a large cystic follicle undergoing atresia.

DISCUSSION AND CONCLUSIONS

1. Thirty-six patients ranging from 15 to 49 years of age were subjected to laparotomy for various reasons, i.e., fibromyomas, legal sterilization, etc. Among these patients there was one who had delayed menarche (age 15), several with functional amenorrhea, and in one of these it was established that bleeding was anovulatory when it did occur. Gonadotropins were administered in varying doses for several days before laparotomy at a known time of the cycle. In several patients with ovarian dysfunction, such as functional amenorrhea, no evidence of past corpora lutea could be demonstrated in the biopsies nor was a progestinal response of the endometrium obtained following the course of gonadotropins. In the patients with normal cycles, superovulation was occasionally produced and in four instances recently ruptured follicles were discovered at laparotomy. It appeared that more or less similar degrees of stimulation of the ovary could be obtained with anterior pituitary extracts, equine gonadotropins, and also with chorionic gonadotropins if used in sufficient dosage (about 4,000 R.U.). Chorionic gonadotropin when combined with anterior pituitary synergist appeared to yield the most promising results, if the production of corpora lutea was taken as the goal. However, no matter what type or combination of gonadotropins was used, the most apparent histologic change was follicle atresia.

2. Aside from the changes in the follicular apparatus, there occurred important changes in the other components of the ovary, i.e.:

a. Marked theca cell hypertrophy with luteinization;

b. Response of the vascular bed as seen in increased capillary congestion, extravasation of red blood cells into areas of loosened stroma and into the core of corpora atretica as well as in degenerating corpora lutea;

c. Indistinct activation of patches of cells in the ovarian stroma;

d. Rejuvenation of the dormant but once active theca cells that were incorporated into the basic substance of the ovary by forming a cellular wreath about the corpus atreticum. These reactivated cells take on a truly "interstitial cell" quality.

It is felt that the reactions in these component parts of the ovary are probably responsible for the occasional beneficial results seen following the use of gonadotropins in certain conditions as functional amenorrhea, oligomenorrhea, some types of dysmenorrhea, certain types of mastalgia and menometrorrhagia.

3. Since the prime interest in the employment of gonadotropins is an attempt to rectify ovarian dysfunction which manifests itself as functional menorrhagia or functional amenorrhea or sterility, the impression has gained currency that these disturbed entities are functional rather than organic. It must be stressed that structure and function are indissolubly linked to each other. The concept of functional disturbance without organic disturbance must be relegated to the scrap heap of obsolete theories.[13] In the evaluation of the histologic changes in the human ovary following the administration of gonadotropins, it must be borne in mind that more or less similar changes are seen in the ovary in some types of dyspituitarism (as in idiopathic hirsutism, certain types of menorrhagia and secondary amenorrhea); in hyperprolanemia (as in hydatid mole or chorionepithelioma); in pregnancy and pubescence;[14] in fetal ovary under the influence of pregnancy.[15]

4. It is evident, however, that orderly follicle maturation and ovulation and corpus luteum formation in patients with ovarian dysfunction was not attained. It is hoped that proper dosage, time interval and combination of gonadotropins may yet yield more desirable results, so that it may be used in the anovulatory sterile woman.

The author gratefully acknowledges the source of the gonadotropins used in this study which were generously supplied by the following pharmaceutical organizations: Extract of the anterior pituitary as gonadotropic factor by Armour and Co.; equine gonadotropin as gonadogen by the Upjohn Co.; chorionic gonadotropin as pranturon by Schering Corporation; combined chorionic gonadotropin with anterior pituitary synergist as synapoidin by Parke, Davis and Co. Other gonadotropins such as gonadin (Cutter), anteron (Schering), and prephysin (Chappel) were also used. The stilbestrol, as synestrol, was supplied by Sharpe and Dohme.

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THE SIGNIFICANCE OF FETAL ENVIRONMENTAL DIFFERENCES

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THE existence of a profusion of myths and superstitions has probably somewhat inhibited until modern times scientific thought and investigation into maternal-fetal relationships from the standpoint of how fetal development may be influenced by varying maternal factors. During the last twenty years, however, many facts and some very interesting hypotheses have accumulated in the literature of various fields—medicine, physiology, psychology, and biochemistry. The level of hormones in the mother's blood, the presence of drugs or toxins, the presence and level of certain food elements may all be thought of in the broader sense as constituent parts of the fetal environment. So also may such sounds or mechanical pressures as are perceptible to the fetus, and such maternal factors as emotional state, physical activity, fatigue, etc., which may alter in any way maternal blood levels of hormones, food elements, waste products, or oxygen.

Together such factors represent an environment as complete and probably fully as important as the social, physical, nutritional, and other components of the environments of infants or children. Since the period of intrauterine life is the period of actual formation of almost all adult structures, adverse environment during this time would undoubtedly occur more frequently and be of much greater eventual importance than at any other period were it not that the fetus is in certain ways protected by factors which tend to maintain at a near constant level, many environmental constituents. The homeostatic characteristics of the mother's body and its ability to maintain within narrow limits such blood constituents as chlorides, sugar, amino acids, calcium, phosphorus, iron, etc., eliminate many environmental extremes. The barrier offered by the placenta to certain substances protects against many infectious organisms and agents. The protection offered by maternal abdominal wall, uterus, and the amniotic fluid to mechanical and sound stimulation

assures that many minimal stimuli of this sort are lost to the fetus. These protective mechanisms reduce the range of environmental differences and eliminate many of them. That many such changes and differences do remain, however, is undeniable, and I shall discuss some of these and their significance in the following pages.

NUTRITION

Attempted reduction in weight of the fetus by restricting maternal diet, in order to facilitate ease of delivery, is a procedure which still enjoys some popularity in certain sections of the country. This procedure has enjoyed little or no success because the fetus acts as a parasite and, if necessary, satisfies its nutritional needs at the expense of the mother's body.

According to Adair[1] and others, the growth of the fetus seems to be independent of fats and carbohydrates in the maternal diet, as long as the diet is not grossly deficient in total calories. Restrictions of diet are effective in controlling fetal weight only when so drastic as to reduce materially the mean levels of maternal blood sugar, amino acids, and perhaps fatty acids, a situation met with only in partial starvation. Jonen[2] and others have been able to produce animal fetuses of abnormally low birth weight through actual starvation of the mother with marked depletion of her tissues during pregnancy. In case of starvation even those mechanisms for the maintenance of normal amino acid and sugar levels in the blood fail, and, since the whole diffusion mechanism is dependent upon relative levels in the maternal and fetal circulations, the amount of nutritive materials transmitted through the placental membrane is decreased. In diabetes where the mechanism for maintaining a normal basal blood sugar level is incapable of functioning, there is a deposition of additional quantities of fetal fat, although here there is some question as to an aberrant function of the pituitary gland contributing to the production of the excessive weight.

Maxwell[3] has shown that in starvation maternal mineral reserves may be so depleted as to produce a condition of fetal rickets. Wolfe[4] reports that the teeth of such infants are also defective. Adair[1] and Geller[5] says that vitamin deficiencies in the mother's diet may seriously injure the fetus. Rector[6] and others have shown that a vitamin D deficiency during pregnancy predisposes the child to early rickets. I have recently had occasion to examine the skeletal x-rays of a large group of breast-fed infants taken at one month of age, whose mothers, living in the slums of a large city, suffered from rather severe malnutrition during pregnancy particularly as regards vitamin D and milk. The incidence of active and well-developed rickets in this breast-fed group at the age of one month was very high. Guggisberg,[7] on the other hand, has demonstrated that young rats whose mothers received large doses of irradiated ergosterol during the period of gestation were extremely resistant to rickets. Sontag and Munson[8] have demonstrated that vitamin D fed in moderately excessive amounts will produce overly mineralized bones in the fetus, and extremely excessive amounts will produce demineralization. Scurvy tends to appear earlier and in a much more malignant form in infants whose mothers' diets were grossly deficient in vitamin C. Hale[9] has stated that pig fetuses born of mothers fed a diet grossly deficient in vitamin A are born with defective eyes and are permanently

blind. He has also found a very high incidence of defects of the palate in fetuses from his low vitamin A mothers. Warkany[10, 11] has shown that rats born of animals on a grossly deficient diet usually had deformities of the long bones, sternum, or mandible. It seems not impossible that diets grossly defective in certain of the essential amino acids may in part be responsible for the defective embryonic development of certain fetal tissues. Murphy and Bowes[12] have investigated this possibility but without definite conclusions.

The intrauterine sensitization of the fetus to food allergens does occur, according to Ratner[13] and his co-workers who have produced a good deal of evidence of this phenomenon. It seems not unlikely that many of the eczemas, asthmas, and allergic gastrointestinal reactions of early infancy are the result of intrauterine sensitization. Ratner believes that such intrauterine sensitization tends to occur from the excessive use of certain foods by expectant mothers who have allergic tendencies.

It is possible also that the physical stamina or constitutional adequacy of a newborn infant may depend to some degree upon the adequacy of its mother's diet and her body stores of certain of the vitamins and amino acids. Roentgen examination of a group of newborn infants has shown that the severity of round bone scars resulting from the birth process is very much greater in those children born of mothers whose diet was *grossly* defective in the muscle- and gland-building elements and in vitamins. This fact suggests that children from inadequately nourished mothers may suffer a greater neonatal growth interruption than will those of well-nourished mothers.[14, 15]

TOXINS AND DRUGS

Mosher[16] has found that mapharsen, quinine, or sodium salicylate when fed or injected into pregnant animals, produces hemorrhages in the labyrinth of the fetuses without producing similar hemorrhages in the mother. Mapharsen produced the greatest hemorrhages which were located in the scala vestibuli, vestibule, and semicircular canals. Taylor[17] has reported an increased incidence of congenital deafness among the offspring of mothers who, during the malaria season, were heavy users of quinine. He attributes this high incidence of deafness to the effects of quinine upon the fetal inner ear. Mosher's work lends some credence to these observations, although doses used far exceeded those which normally are used therapeutically in human beings. Adair and Stieglitz,[18] however, have observed no harmful effects from quinine. Burnett[19] and Pettey[20] have reported morphinism in the infants of mothers who were habitual morphine users.

THE ENDOCRINE GLANDS

The interrelationship of the maternal and fetal endocrine systems constitutes an interesting subject for study. It is generally accepted that the fetal and maternal endocrine systems function to some degree at least in a complementary fashion. The work and writings of Rupp,[21] Soule,[22] Hamblen,[23] Schlossman,[24] and many others have amply demonstrated that the two endocrine systems complement each other. This complementary relationship is well demonstrated when pregnancy is

complicated by diabetes. Heilberg[25] found a marked increase in the number of islands of Langerhans in the fetal pancreas when mothers were diabetics. Gray and Feemster[26] found the insulin content of the pancreas of fetuses of diabetic mothers twenty-four times as high as that in the mother's pancreas. Weiner[27] found that the pancreas of infants of diabetic mothers contained much more insulin than did those of infants of nondiabetic mothers. Gordon[28] and others have reported an improvement in diabetic mothers during pregnancy presumably due to the passage of fetal insulin into the maternal circulation. In such cases the newborn infants usually developed a marked hypoglycemia as a result of the compensatory hyperfunction of its pancreas.

Teel,[29] Hain,[30] Sontag and Munson,[31] Watts,[32] and others have shown that by the introduction of large doses of Evans' growth hormone to pregnant rats during the last two weeks of the period of gestation it is possible to produce rat fetuses which are larger than control animals. Hamilton and Wolfe[33] report that they injected testosterone propionate into pregnant animals with the result that females in the litters from these animals showed retardation of sexual development. Arnold[34] claims to have been able to influence the weight of the human fetus by the administration of thyroid to mothers during their last months of pregnancy. Patterson, Hunt, and Nicodemus,[35] and others have demonstrated that in patients with low thyroid function the secretion of the fetal thyroid gland supplements to some degree the production from the maternal thyroid. These and many other examples indicate that fetal and maternal endocrine glands act as complementary production units. Such a complementary endocrine relationship immediately stimulates speculation as to what may be the effects both neonatally and later upon the thyroid function of human infants born of mothers with thyroid deficiency or hyperfunction during pregnancy. Might not maternal hypothyroidism throw an excessive load upon fetal thyroid with a resulting hyperplasia, hypertrophy, and an over-functioning thyroid at birth? Conversely, might maternal hyperthyroidism depress fetal thyroid function? Patterson, Hunt, and Nicodemus[35] have reported that the first of these phenomena does occur, that children of hypothyroid mothers have hyperplastic thyroid glands at birth. As already stated, infants with over-functioning islands of Langerhans as a result of maternal diabetes exhibit a marked hypoglycemia within a few hours after birth. A gradual adjustment of insulin production then takes place. What happens to the endocrine economy of children with hyperfunctioning thyroids as a result of maternal hypothyroidism and what is their developmental history? Patterson and others[35] believe that some congenital goiters are the result of fetal thyroid hyperplasia from maternal absorption of fetal thyroxin production. They believe that these thyroids which are hyperactive at birth undergo an involution within a few months and usually function normally thereafter. The evidence on this subject is as yet inadequate to justify any positive statement as to what effect upon the thyroid economy of a child hypo- or hyperthyroidism of its mother during the gestation period will have. The amount of nonthyroxin iodine in the mother's blood, the severity of the mother's thyroid abnormality, and perhaps other factors may in many instances alter the picture greatly. That such a maternal thyroid disturbance does affect fetal thyroid development and function and may be a very important factor in establishing the level of postnatal thyroid function seems probable.

I have observed a few cases of hypothyroidism during pregnancy in which the newborn infant had a somewhat retarded skeletal development and was inactive, lethargic, and retarded in its behavior pattern. Within a few weeks after birth a sharp spurt in the development of ossification centers occurred together with rapid growth in length and a marked change in the behavior pattern, toward more activity and alertness. One interpretation of these cases is that these infants during their intrauterine lives had been producing thyroxin at a very rapid rate but since each had had to supply not only its own thyroxin needs but part of those of a "poor relative," it had not been able to do both jobs adequately. However, when birth destroyed the maternal-fetal relationship, each fetus was producing an excess of thyroxin over its normal neonatal needs and during the course of a very few weeks the effects of this more than ample thyroid secretion rapidly became apparent in the growth spurt and behavior changes already described. Such material is obviously inadequate to justify any conclusion. This growth spurt appeared to level off during the course of a year, suggesting an adjustment of thyroid function to a level of infant needs. Whether this adjustment always occurs or whether in some instances in children who have an inadequate iodine intake the thyroid sometimes undergoes degeneration with resulting cretinism, as has been suggested by Patterson,[36] is a subject for further investigation.

Experimental work on the effects of excessive amounts of the thyrotropic element of the pituitary in the mother's blood upon fetal thyroid has been reported (Grumbrecht and Loeser[37]), of the gonadotropic hormone on the fetal ovary[38] and of the suprarenal gland upon the fetal ovary (Tanioka[39]). The work is not conclusive and is inadequate to justify an assumption that maternal hyperthyroidism could be expected to cause changes in the development and function of the fetal thyroid. That such maternal thyroid overfunction may produce a depressing effect upon the developing fetal thyroid is, however, a distinct possibility.

OTHER FACTORS

Hooker[40] has shown that the human fetus is capable of responding to tactile stimuli eight and one-half weeks after the fertilization of the egg. Peiper[41] in 1925 reported instances of sound perception and movement responses by the human fetus, as did Ray.[42] Spelt,[43] in 1938, reported the successful conditioning of the human fetus to sound stimuli. My colleagues and I have for several years been investigating the factors influencing fetal activity level and producing an activity response. Deeply disturbed maternal emotion produces a marked increase in activity of the fetus probably as a result of increased adrenalin level in the maternal and, therefore, the fetal blood. Severe maternal fatigue increases fetal activity probably through changes in maternal and, therefore, fetal blood chemistry. The startle reflex is active and a sound of proper pitch, intensity, and proximity will produce an instantaneous and convulsive movement probably through auditory nerve stimulation by bone conduction. These findings have all been mentioned in pre-

vious reports (Sontag and Wallace;[44] Sontag and Richards[45]). The significance of these various stimulating factors in terms of the physiologic, anatomic, and behavior patterns of the newborn infant is less well understood than are their immediate effects. Such stimuli must be very common. My associates and I have had mothers complain of marked fetal activity from the vibration of a washing machine and from piano concerts. Reports of increased fetal activity to the degree of maternal discomfort are not uncommon during violent emotional upsets. We have found activity levels differing as much as 1000 per cent in various fetuses over the last three months of pregnancy.

For a number of years we have been studying the differences in physical and behavior characteristics of fetuses at birth in relationship to their activity prenatally and have made the following observations.

1. The fetuses which had been very active during the last two months of their intrauterine life from maternal emotional distress, fatigue, or other causes, tend to be light in weight in relationship to their length, and show a minimum amount of fat storage. It seems probable that sugar which in an inactive fetus would be converted and stored as fetal fat is burned for energy production in the active fetus (Sontag[46]). The diffusion mechanism of the placenta is such that a completely compensatory increase for an unusual demand for sugar does not occur because of the fetus's mechanism for maintaining basal blood sugar level. Increased transmission of sugar through the placenta is dependent upon an increased disparity between maternal and infant blood sugar levels.

2. There is some evidence, not yet conclusive, that the motor development of fetuses which have been active during the latter half of pregnancy is more advanced during the first year than is that of inactive fetuses (Richards and Newbery[47]). The differences are measured by means of responses to the Gesell schedule at six and twelve months. One possible explanation of this finding is that the increased use of the nervous system during the period of myelinization facilitates the development of the nervous system. Animal experimentation suggests that the myelinization of specific nerves can be accelerated by stimulation of the nerves, and there is, of course, considerable relationship between the function of a nerve fiber and its state of myelinization.

I have, I believe, observed a relationship between some of the early feeding difficulties of infants and prenatal stimulation. In these instances disturbances of gastrointestinal motility, tone and function, manifested by excessive regurgitation, dyspepsia, and perhaps by diarrhea, may have resulted from the development prenatally of an irritable and hyperactive autonomic nervous system. Irritable or poorly balanced adrenergic-cholinergic systems probably constitute an important part of the rather poorly defined syndrome commonly labeled constitutional inadequacy or nutritional diaphysis. Early feeding difficulties based upon motor and secretory abnormalities of the gastrointestinal system are in many instances of autonomic origin. The presence of feeding difficulties of a motor or secretory nature from birth must presume their etiology and basic disturbances during intrauterine life. In prenatal development of such a condition, prolonged nervous and emotional dis-

turbances of the mother during the later months of pregnancy seem to be important. Any such effect must, of course, depend for its mechanism upon changes in the chemistry of the mother's and therefore the fetus's blood as a result of these emotional changes since it is only in such a manner that central nervous system stimulation in the mother could affect the fetus. Acetylcholine and adrenalin are two substances either or both of which may well be involved. Preliminary experiments suggest the importance of acetylcholine. Whatever the chemical change responsible, the autonomic nervous systems of infants born of mothers under such conditions frequently show several evidences of autonomic instability. In addition to regurgitation, diarrhea, or constipation, they may show greater than average heart rate ranges, vasomotor instability or changes in respiratory pattern. Those cases in which a major disturbing factor was known to have occurred and been present for a considerable period of time during later months of pregnancy were recently selected from our group. In one instance, the husband of the woman became insane midway in the pregnancy but continued to live with the wife, although frequently violent and never entirely rational. In another, the mother was an unmarried woman of thirty-five who had suddenly learned that the father of her child, to whom she had expected to be married, was already a married man. To add to her distress her very severe family made life entirely miserable for her. In the eight cases where emotional distress was most obvious and existed over a long period of time, seven infants had moderate or severe feeding difficulties in the form of inability to retain food. In some of these cases there was a tendency to frequent stools for several months. Such observations stimulate speculation but are, of course, inadequate to substantiate the explanation offered here of the origin of some of the early feeding difficulties encountered. The possibilities are intriguing, however, and seem to justify further study.

SUMMARY AND CONCLUSIONS

The evidence available in the literature from both animal experimentation and the observation of pregnant women and the children they bear are indications that differences in environment during the fetal period may be of great importance in the development of the child both before and after birth. Such factors as the drugs women use during pregnancy, their nutrition, endocrine status, emotional life and activity level during gestation may contribute to the shaping of physical status, behavior patterns, and postnatal progress of the children they bear.

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THE COMPLICATIONS OF IRRADIATION TREATMENT OF CARCINOMA OF THE CERVIX*

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THIS is a study of 320 patients treated for carcinoma of the cervix during the years 1936 to 1940 inclusive, at the Ontario Institute of Radiotherapy, Toronto General Hospital, under the direction of Dr. G. E. Richards. It is almost universally true that 65 to 70 per cent of patients suffering from carcinoma of the cervix do not come for treatment until the disease has progressed to Stage III or Stage IV, so that the hope of increasing the salvage rate depends on carrying irradiation treatment to a point sometimes beyond the tolerance of the adjacent normal tissues. The complications of irradiation treatment which may result are of growing concern to all who are taking part in the treatment of patients suffering from carcinoma. Two types of reaction are met with: the acute or inflammatory, which occurs because of proximity of tissue, and the late or fibrotic, which may with extreme vascular sclerosis pass on to a state of necrosis.

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In the hope of improving the results, our routine of treatment has been altered considerably during the last five years. In 1936, radium was administered in massive doses, 8,400 mg. hr. within the uterine cavity and on the vaginal aspect of the cervix. The application was made either with a gold T-tube or with a Swedish box per vaginam and platinum tubes intrauterine. This was supplemented by fractionated high voltage therapy at 200 k.v. to 1,400 r. on 4, 6, and 8 ports and 900 to 1,200 r. on a perineal port. Many times a second high voltage series was given in from three to six months.

In 1937, we began to fractionate the radium treatment after the manner of Regaud and the high voltage treatments were routinely given before the radium was applied.

METHOD

Early in 1938 new apparatus inaugurated high voltage treatment at 400 k.v. thus permitting more efficient depth dosage in heavier women. The routine became 2,400 r. on each of four ports and 900 r. on the perineum. High voltage treatment was repeated in a number of patients. Radium followed the primary high voltage series in the Regaud method. This routine was continued throughout the greater part of 1939, and the results of treatment were the best in the records of the Institute.

Late in 1939, a vaginal cone was adopted instead of the perineal port to supplement the pelvic high voltage cross-fire. By this means, a dose of 3,000 r. was delivered directly on the cervical area. A central posterior field was added or, in very heavy women, two lateral fields. Physical charts showed that the depth dose had a very satisfactory concentration and distribution. The immediate effect was impressive in the rapidity with which advanced lesions responded, but as will be seen complications have arisen and a revision of the method is indicated.

There has been much speculation as to the cause of the variation in response to irradiation. In tumors, the importance of cell type and degree of cell dedifferentiation have been emphasized. We have never been impressed by this theory. The same variation appears in the mal effect of irradiation on the normal tissues of different individuals. Is it not possible that radiosensitivity is personal rather than inherent in the tumor cell? In this present study, comparable patients received approximately the same irradiation and in some the results were satisfactory while in others the damage to normal tissue was irreparable.

Radiation sickness, cystitis, and proctitis are all fairly frequent developments during or immediately following treatment. Occasionally, they have interfered with the course of therapy. Nausea usually responds to a combination of nembutal, liver extract, and vitamin B. Cystitis is much less frequent when a self-retaining catheter keeps the bladder empty during radium treatment and the careful placing and packing off of vaginal applicators and the avoidance of central high voltage ports will prevent unnecessary injury to bladder or rectum.

Fever and infection during the course of treatment have caused much concern. Routine cultures are taken from the cervix because of the

danger of streptococcal infection. In the last five years, cultures have been taken from 243 patients, and of 47 with positive hemolytic streptococcal culture, 25 developed some complication subsequently, such as excessive pyrexia, vaginitis, pyometria, cellulitis, thrombophlebitis, pelvic abscess, peritonitis and septicemia. Recognizing this danger, we altered the order of treatment, high voltage therapy being given before radium. As a result, it was observed that 14 patients of the remaining 22 developed negative streptococcal culture during the preliminary treatment. This left a small group of 8 patients in whom trouble did not develop in spite of a positive culture. Other mishaps prompted the routine of anaerobic culture. Of 176 patients having such cultures taken, 72 showed positive anaerobic streptococcal culture and 32 of these developed inflammatory complications. This suggests that the anaerobic organism is more frequently present in the cervix and vagina but is not so pathogenic. The cultures from 129 patients were negative and only 28 of these developed any inflammatory complication. In all, 4 of the 5 deaths attributed to treatment prior to 1940 were due to postoperative infection, following the introduction of intrauterine radium. Three of these patients died of peritonitis and one of septicemia.

The rectum is the most exposed to injury from irradiation of any part of the intestinal tract. The frequency with which postirradiation proctitis is encountered has already been suggested. It is a condition which ordinarily disappears within a few weeks and as a rule is not followed by more serious and chronic sequelae. The typical late irradiation lesion is rectal ulceration. The late T. F. Todd,[1] of Manchester, wrote an excellent description of this condition outlining the two types, intrinsic, that is primary chronic ulceration of the rectum, or extrinsic which is characterized by massive perirectal cellulitis and stenosis of the rectum as a result of which ulceration develops. He recalled the term "pseudocarcinoma of the rectum," a condition which in our experience has necessitated biopsy a number of times to establish the diagnosis.

Eleven of the 36 patients treated in 1936, when massive doses of radium were given, developed primary proctitis. In 1937, 1938, and 1939, when the high voltage irradiation was increased and the radium fractionated, this complication was relatively less common, but late ulceration became more frequent. In all, 12 patients have had rectal ulceration, half of them with associated cellulitis and stenosis. The longest period between treatment and ulceration was two years. One patient required colostomy and another bled so profusely that her hemoglobin went down to 15 per cent.

Pemberton,[2] in a paper published in 1932, described irradiation injury primarily as an injury to the mucous membrane, generally occurring at fixed points, such as the rectum, sigmoid, and cecum, and to the small intestine when adherent. Stenosis often follows. T. E. Jones[3] warns that one should always keep in mind the possibility that symptoms simulating intestinal obstruction several months or years after irradiation are due to stricture rather than metastases and that investigation should be thorough before high voltage therapy is given. One patient treated by us last year suffered because the significance of these symptoms was not appreciated.

The first example of bowel injury we encountered in this series was at post mortem in 1936 when a patient dying of hemorrhage after moderately heavy high voltage therapy showed extensive ulceration of sigmoid and rectum. In 1940, however, when the high voltage depth dose was the heaviest, we have to report a number of patients who suffered intestinal injury. Two patients died from postirradiation ulcerative colitis. One of these at post mortem showed complete absence of tumor but the walls of the colon and rectum were thick and edematous, and there was complete loss of the mucosa with ulceration penetrating to the muscular coat of the bowel. Three patients died of intestinal obstruction and one of these at post mortem showed irradiation reaction of the whole intestine below the jejunum. The terminal ileum had two perforations and was bound by adhesions, and in this case also the tumor had completely disappeared.

In 1933 Behney,[4] in a review of autopsies in advanced carcinoma of the cervix, reported three cases which deteriorated rapidly after irradiation and died. At post mortem there was extreme sloughing of pelvic tissues and only one showed any trace of carcinoma. Death came from overwhelming intoxication probably due to too vigorous treatment. Two patients of ours who died in 1940 directly following treatment seem to correspond to this type. One had a Stage IV carcinoma and received 1,500 r. on 5 ports at 400 kv. and 3,000 r. at 180 kv. via the vaginal cone. The immediate effect was excellent. The local tumor healed and the parametrial extension was appreciably lessened. Five days later she received full radium treatment and shortly afterward began to run a fever and went rapidly downhill to die within ten weeks. Post mortem showed massive fibrosis of large and small intestine, ulcer of rectum and necrosis of vagina, a pelvic abscess in the center of the adherent mass. The only remains of tumor were small microscopic islands. The second patient also had Stage IV with rectovaginal fistula. She died three days after completing high voltage at 400 kv. 1,800 r. on 3 posterior ports and 2,100 r. on 2 anterior ports. Post mortem showed sloughing of the whole upper two-thirds of the vagina, fibrosis and thickening of the pelvic cellular tissue, bilateral hydroureter and hydronephrosis. All trace of a pre-existing tumor was gone.

Two patients, who still survive, also presented interesting histories. The first, treated in 1939, developed a tender mass in the right lower abdomen fifteen months later. Shortly after, there was a discharge of pus from the vagina and, because the mass was in the appendiceal region, a laparotomy was performed and a postirradiation adherent fibrosis of cecum and terminal ileum with abscess formation was found, apparently the result of necrosis. No evidence of active tumor was seen. The second, after high voltage therapy at 400 kv. to give 1,800 r. on 6 ports and 3,000 r. per vaginal cone at 180 kv., received 7,340 mg. hr. of radium by the Regaud method. Considerable difficulty was experienced in dilating the cervix, and this may have been the factor which caused the development of massive postirradiation cellulitis. Consequently, intestinal obstruction developed, but after an extremely severe illness, the Miller-Abbott tube and Wangensteen drainage, in the hands of a persistent resident, were successful.

It is often difficult to decide the true nature of urinary tract complications. Distortion of the base of the bladder with displacement of the ureteral openings is commonly observed, even when the tumor is entirely confined to the cervix. As a consequence, the evacuation of the bladder may be interfered with and the flow of urine from the ureters obstructed. Therefore, cystitis is not uncommon and hydroureter and hydronephrosis occur many times in the absence of symptoms. As disease progresses and the cellular tissues become involved either by invasion by tumor or by associated cellulitis, the tendency toward ureteral obstruction is much greater. As long ago as 1858, Wagner noted that ureteral dilatation was present in one-third of the individuals examined post mortem. Seventeen, of the 24 autopsies held on patients in this series of cases, showed ureteral obstruction, hydroureter and hydronephrosis or pyonephrosis. In every case, the obstruction was due to malignant infiltration of the cellular tissue. We have not encountered stricture of the ureter in a "cured" case of carcinoma of the cervix when it was not present before treatment was undertaken.

Late ulceration of the bladder is very similar to the ulceration of the rectum. We had had three cases late in onset, eighteen months to two years after irradiation. Clinical manifestations are dysuria and frequency with hematuria. The ulceration is very hard to differentiate from malignant necrosis and biopsy was required in every case.

One is impressed with the need for thorough examination of the urinary tract in all cases. A number of times cystoscopic examination has discovered secondary carcinoma of the bladder and so changed the classification of tumor to Stage IV. Pyelograms are indicated in those cases where difficulty is experienced in catheterization of the ureters. We take a nonprotein nitrogen routinely on our patients and have been surprised to find that, apart from impending uremia, it is rare to see the level above normal. We are intending to use the two-hour test as the criterion of damage to kidney function. By this routine, the condition of the urinary tract prior to treatment will be established.

Six of our patients developed vesicovaginal fistula. Our experience has been that of Graves,[5] Cutler, Smith and others that bladder fistula in carcinoma of the cervix is a manifestation of progressive disease. Eight patients developed rectovaginal fistula, and we felt this also was due to invasive tumor.

In 1927, Baensch of Leipsig reported the first case of spontaneous fracture of the neck of the femur following roentgen treatment of carcinoma of the cervix. The number of cases reported in the literature has increased until in a recent publication Strauss and McGoldrick[6] were able to collect 59. The incidence of this serious complication is variable. Dalby, Jacox and Miller[7] reported, in 1936, 14 cases which they had personally observed, while many men of experience have not encountered it or state the incidence as low as one in a thousand or one in two thousand treated cases.

The pathologic features of spontaneous fracture of the neck of the femur are that it develops in the superior portion of the head of the femur close to the neck as a result of vascular sclerosis with consequent osteoporosis. There is no new bone formation and secondary carcinoma

is not found at the site of fracture. Clinically, the condition manifests itself on an average of seven months postirradiation. The actual fracture is preceded by pain in the hip radiating into the thigh and knee. The diagnosis is made by x-ray.

The average age of the patients reported by Dalby and his associates was fifty-seven years. Bilateral fracture occurred in three cases. Eight of their 14 patients had metastatic involvement of the bony pelvis or the other femur. After ten months, x-ray showed 9 patients with fibrous union sufficient to allow partial function but none showed callous formation.

Strauss and McGoldrick suggest that lateral fields are largely responsible for the accident, but it is interesting to note that in the large series of Dalby, Jacox, and Miller the high voltage therapy was at 200 kv. and on 2 anterior and 2 posterior ports to give from 1,500 r. to 2,000 r. per port.

None of our patients in this series of cases experienced spontaneous fracture of the femur.

We have included 17 cases of carcinoma of the cervix which developed at least two years after supravaginal hysterectomy. It is encouraging that the salvage rate in this type of case promises to be considerably higher than when treatment is given for carcinoma of the cervix with the body in situ. This is in keeping with the results reported from other clinics.[8, 9] It has been suggested that there was more risk of injury to adjacent tissues in treating carcinoma of the stump of the cervix. For example, there is always the possibility of adherent intestine after abdominal operation. Our series of cases has been entirely free of major complications.

CONCLUSIONS

1. If a lethal irradiation dose is to be delivered to carcinoma wherever it may be, whether in the primary site or extending out widely into the pelvis, there is always the danger of irradiation beyond the tolerance of adjacent normal tissue.

2. In the treatment of carcinoma of the cervix by surgery, certain complications are accepted as frequently associated with this form of treatment. Is it not reasonable to accept some of the complications which have been described as part of the risk in the treatment of advanced cases which are quite beyond the scope of any other form of treatment?

3. The lesson to be learned from an appreciation of these complications is that we are feeling our way toward an ideal method of irradiation treatment and must be guided by our failures as well as by our successes.

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Medical Arts Building

ANHYDRO-HYDROXY-PROGESTERONE IN THREATENED INTERRUPTIONS OF PREGNANCY

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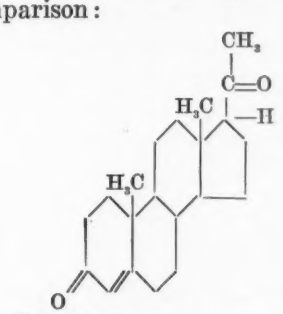
MANY factors must be considered in any careful study of spontaneous abortion or miscarriage. On the part of the mother, local and constitutional physical abnormalities, derangements of the nervous system and the emotional state and deficiencies or dysfunctions of the endocrine system must be evaluated. Variations from normal in embryologic development, which includes errors in implantation and growth or fetal deaths for a variety of reasons, must be realized also as factors of importance.

Maintaining a constant realization that all of the aforementioned factors must be taken into consideration in possible therapeutic prevention of abortion, it is the purpose of this paper to discuss the results of a series of threatened interruptions of early pregnancy treated with anhydro-hydroxy-progesterone.

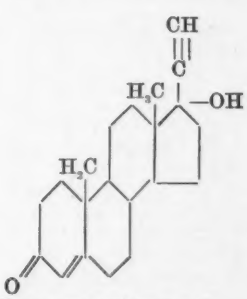
The role of the corpus luteum and its hormones in the cycle of the development of the human ovum and in the physiology of nidation and development of the fertilized ovum, is generally well understood. The clinical use of corpus luteum extracts and progesterone has been discussed by Falls, Lackner and Krohn,[1] Kane,[2] Elden,[3] and Campbell and Sevringhaus.[4] The general consensus of opinion of these observers is that progesterone therapy is of unquestionable value in the treatment of threatened abortion. However, Hamblen[5] in a recent article reported the results of a series of patients with histories of repeated abortions. These patients were treated with progesterone alone or with progesterone and estrogens, or progesterone and chorionic gonadotropins or anhydro-hydroxy-progesterone. He concludes that "this therapy fails to prevent abortion. There is a likelihood that large doses of progesterone may precipitate abortion by depressing intrinsic progestin."

The desirability of an oral preparation is obvious. Progesterone itself must be administered by injection, because it is practically inactive when given orally. Hohlweg and Inhoffen[6] succeeded in modifying the molecule so that a compound was obtained with progestin action which was effective when given by mouth.

The formulas of progesterone and of the new compound are given for comparison:



Progesterone



Anhydro-hydroxy-progesterone

It will be noted that the modifications of the progesterone formula consist of attachment of a hydroxyl group directly to carbon atom-17 and the removal of the elements of water from the acetyl group. On this account the compound is termed anhydro-hydroxy-progesterone. Another chemically descriptive term is pregnen-in-ol-17-on-3.

OBSERVATIONS

A series of 26 cases of threatened miscarriage is reported. In 16 of the patients in this series, the threatened interruption of pregnancy was associated with bleeding. Twelve of these patients with bleeding carried on to term with successful delivery. Four miscarriages occurred.

In 4 of the patients in this series, the threatened miscarriage was not associated with bleeding, but painful uterine contractions were present. Clinically the diagnosis was justified. In none of these patients was the pregnancy terminated prematurely.

Great care has been exercised to limit the diagnosis of "threatened abortion" in this series. Many patients with low abdominal pain or discomfort simulating "pre-menstrual tension" have been treated with oral progesterone but are not included.

In an effort to evaluate therapy without reservations, additional medications and procedures were minimized. Bed rest with bathroom privileges was advised. A mild barbiturate was usually prescribed for sleep at night. Laxatives and cathartics were prohibited. A light diet was given. The use of narcotics, heavy barbiturate sedation, ice bags, and elevation of the foot of the bed were omitted.

Many of these patients were receiving thyroid at the time of onset of symptoms. In such cases, the thyroid dosage was not changed.

TABLE I. TIME OF THREATENED INTERRUPTIONS OF PREGNANCY

GESTATION IN WEEKS	NUMBER OF CASES
4	1
6	1
8	7
10	1
12	3
14	1
16	2
20	4
At time of expected menstrual period	17
Not at time of expected menstrual period	3

TABLE II. PARITY OF PATIENTS WITH THREATENED MISCARRIAGE

Primigravida	12
Gravida II with previous normal course	1
Gravida II with previous bleeding or miscarriage	2
Gravida III with previous normal course	1
Gravida III with previous miscarriage	2
Gavida IV with previous normal course	1
Gravida IV with previous miscarriage	1

It is noted from Table I that 17 of 20 patients presented symptoms of threatening miscarriage at approximately the time of an expected

menstrual period. Thirteen of the 20 cases occurred at or before the twelfth week of gestation.

Twelve of the 20 patients were primiparas. Of the 8 multiparas, 5 had had at least one previous miscarriage and might be considered as possible habitual abortion cases (Table II).

Each of these patients had already had a physical examination. Blood pressure, urine examination, blood counts, Wassermann or Kahn test and basal metabolism had been performed in all instances as part of our routine work-up.

RESULTS

A series of 20 patients with threatened spontaneous interruption of early pregnancy were treated with anhydro-hydroxy-progesterone and progesterone. Sixteen of the 20 pregnancies (80 per cent of the cases) were maintained to successful delivery at or close to term.

Thirteen of the 20 patients in this series were treated with oral anhydro-hydroxy-progesterone. The dosage varied from 30 to 100 mg. per day and was continued for various periods of time from three days to several weeks. Seven of the patients received combined oral anhydro-hydroxy-progesterone and hypodermic progesterone.

No set rule has been offered for such therapy, and when facing a threatened miscarriage, large amounts of progesterone may be administered without untoward results. In one case, 65 mg. of intramuscular progesterone and 560 mg. of anhydro-hydroxy-progesterone were administered in nineteen days followed by 10 mg. of the orally effective preparation twice a day for three weeks. This pregnancy continued after what was first considered an inevitable abortion.

It is our belief that if sufficient oral anhydro-hydroxy-progesterone be given, it may supplant hypodermic therapy. In our experience, 60 to 100 mg. or more oral anhydro-hydroxy-progesterone in three or four split doses during the first twenty-four hours after onset of symptoms is a therapeutic amount. The usual procedure is to administer 2 to 10 mg. of progesterone intramuscularly once or twice and from there on carry on with oral anhydro-hydroxy-progesterone alone. At this time it may be propitious to emphasize the importance of onset of therapy *immediately* after onset of symptoms. Three of the patients who miscarried in this series, reported the bleeding or cramps more than twenty-four hours after their onset. In these cases, therapy was of no avail. This does not mean that they might have carried on if treatment had been started earlier. A blighted ovum may have been the cause of each case. One patient presented the problem of a bleeding polyp complicating early pregnancy.

When progesterone is being administered prophylactically as in habitual abortion or other conditions where a miscarriage might be feared, 1 mg. should be given every three or four days intramuscularly or 10 to 30 mg. daily if the orally effective preparation may suffice.

Toxic symptoms were not noted in any patient in this series.

It is difficult to evaluate the relative value of the effective oral and subcutaneous dosage of these related preparations. It is our impression that about ten times the effective subcutaneous dose of progesterone is effective when administered orally as anhydro-hydroxy-progesterone.

DISCUSSION

There is a group of individuals not included in this series whose symptoms of low pelvic pressure, insufficient increase in size of the uterus, or temporary decrease in size and increase in irritability of the uterus, indicated a tendency toward a threatened miscarriage. However, the symptoms were not severe enough to classify these individuals as threatened miscarriage.

We have used anhydro-hydroxy-progesterone freely in numerous such cases and with pleasing results. The dosage has varied from 20 to 60 mg. daily. A marked degree of relaxation of the uterus with a rise of 2 to 4 cm. in the McDonald measurement in one week is not unusual. A concomitant improvement in the state of well-being was noted frequently.

It is realized, as mentioned previously, that this is an indefinite clinical group; one with uncertain diagnosis and one which responds well to other forms of therapy such as bed rest and mild sedation. However, the response to anhydro-hyroxy-progesterone is so marked that it is considered worthy of mention.

There has been some discussion relative to the desirability of maintaining a gestation with the prospect of an abnormal child or monstrosity. There has been no such end result in our experience to date. Our feelings are that if the ovum be blighted, it will go on to miscarriage in spite of preventive therapy.

SUMMARY

1. Twenty patients with threatened spontaneous interruption of pregnancy were treated with anhydro-hydroxy-progesterone (oral) and hypodermic progesterone.

2. Care has been taken to limit the diagnosis of threatened miscarriage.

3. Sixteen pregnancies (80 per cent) were maintained with successful delivery at term.

4. Four patients miscarried. In each of these cases, treatment was begun more than twenty-four hours after the onset of symptoms. One of these miscarriages followed removal of a bleeding polyp.

5. Oral anhydro-hydroxy-progesterone has been administered in dosage up to 100 mg. per day. Intramuscular dosage of progesterone varied from 1 to 30 mg. per day.

6. Anhydro-hydroxy-progesterone* seems to prove to be a valuable medication in the treatment of threatened spontaneous miscarriage.

7. No toxic symptoms were noted.

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*The preparation, marketed as "pranone," was supplied by Dr. Max Gilbert of the Schering Corporation.

ORAL THERAPY WITH PREGNENINOLONE IN FUNCTIONAL UTERINE BLEEDING

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FUNCTIONAL uterine bleeding is excessive bleeding due to factors which are not yet known. Many theories and therapeutic agents have been recommended, but none turned out to be entirely satisfactory. One factor, however, seems to be present for uterine bleeding, whether normal or abnormal, namely estrogen stimulation. However, the future may prove the existence of some relationship between the hormones and structural changes in the endometrial vascular supply and that the factors which are responsible for the bleeding are within the endometrium, possibly of vascular nature, and not dependent upon the histologic type of the endometrium.

MATERIAL

This study was conducted on a series of 20 cases of functional uterine bleeding, in which any palpable organic disease could be excluded. According to the clinical type of bleeding, they can be subdivided into 11 cases of puberty bleeding and 9 cases of maturity bleeding.

METHODS

A careful clinical evaluation of the patients, based on a thorough history, physical examination, appropriate laboratory studies and endometrial biopsies was carried out. A quantitative estimation of urinary prolans and estrogens was made in all cases. The prolans were assayed in a morning specimen and the estrogens in a twenty-four-hour specimen. The urinary prolans were extracted by utilizing the modification of Zondek's method. A fresh refrigerated specimen of urine was slightly acidified with dilute acetic acid. Ethyl alcohol was added and the mixture allowed to stand from two to twenty-four hours, then centrifuged and the supernatant fluid discarded. Ethyl ether was added, well shaken in order to break up the precipitate, which removes the estrogenic substances, again centrifuged and the supernatant fluid discarded. The precipitate was dried until all ether had evaporated. Distilled water was added and constantly shaken for ten minutes, again centrifuged and the supernatant fluid saved, which contains the follicle-stimulating hormone. Three immature female mice weighing from 6 to 8 Gm. are injected twice daily for three days. The mice are not injected on the fourth day and are autopsied on the fifth day or one hundred hours after the first injection. The estrogens were extracted by using the Kurzrok and Ratner method. Nine hundred cubic centimeters of the twenty-four-hour urine specimen were made slightly acid with dilute acetic acid, then saturated with sodium chloride. The treated urine is then covered with ethyl acetate to the top of the flask. A second

flask is filled with 200 c.c. of ethyl acetate and attached to the first flask. The hot plate is turned on to medium heat and the ethyl acetate distilled over, and condensed. It drops to the bottom of the first flask from which it returns to the second flask. The drops of ethyl acetate in passing upward through the urine extract the hormone. This provides continuous extraction for forty-eight hours. The extracted urine is then discarded and the ethyl acetate extract, which contains the hormone, is concentrated by vacuum distillation. To the remaining substance, 6 c.c. of propylene glycoll are added. This solution is then injected into ovariectomized rats. The animal assay consists of injecting a definite dosage of the solution in three equal doses, and twenty-four hours later making a vaginal smear. A positive smear must show the cornified cells characteristic of estrus.

In order to determine the effect of pregneninolone on the endometrium, pretreatment endometrial biopsies were taken, by suction curettage, and several biopsies after oral therapy in all the cases where no contraindication to take an endometrial biopsy was given.

DOSAGE

In 1938 Inhoffen and Hohlweg prepared a derivative of progesterone, which was identified as pregneninolone. When given orally to immature mice previously treated with estrogens, it was approximately 15 times as potent as progesterone given orally, while given by injections to similar animals, it was only one-third as effective in producing progestational changes as was synthetic progesterone. The question we were most interested in was the possibility of affecting the endometrium by oral corpus luteum hormone therapy, the dosage necessary, and the influence of our therapy on the bleeding. According to individual authors, the doses required for the conversion of a proliferative endometrium into its secretory phase are different. Kaufman uses 60 mg., Zondek 40 to 45 mg. of corpus luteum hormone by injection, while our own investigations showed the need of about 40 mg. of corpus luteum hormone. Our own data on oral pregneninolone* therapy show that we need from 280 to 350 mg. to stop the bleeding and to obtain progestational response of the endometrium. This would mean that we need from six to seven times the injected dose when given by mouth. Similar good results in functional uterine bleeding with oral corpus luteum therapy have been reported by Clauberg, Ustuen, Wenner, and Lauterwein. Hamblen and co-workers report good results after oral use of pregneninolone in functional menometrorrhagia.

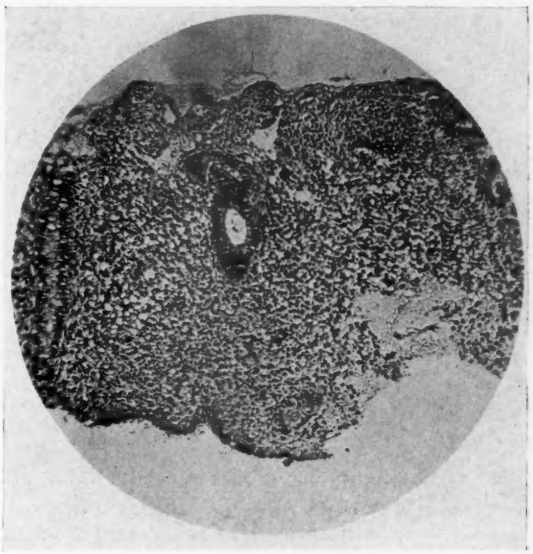
CASE REPORTS

Juvenile Bleeding.—

CASE 1.—A. S., a white 18-year-old girl, had episodes of metrorrhagia for two years. Onset of period at 14 years of age and occurred every twenty-eight days, lasting for four or five days. A year and one-half ago curettage had been performed to check severe hemorrhage. Prior to consultation in clinic, patient bled for six weeks continuously. Genitals were normal. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone 10 R.U. per day. Follicle-stimulating hormone was negative.

*Progesterol (Brand of pregneninolone) 1 tablet = 10 mg., was supplied through the kindness of Dr. Leo Pirk of Roche-Organon, Inc., Nutley, N. J.

Therapy: Three hundred milligrams of pregneninolone were given over a period of six days in daily doses of 50 mg. Bleeding stopped on the fifth day. Endometrial biopsy, done on the ninth day after therapy started, showed some degree of progestational alteration. Subsequently an oral dose of 240 mg. of pregneninolone, given during the second half of the cycle, established a regular menstrual cycle for the last six months.



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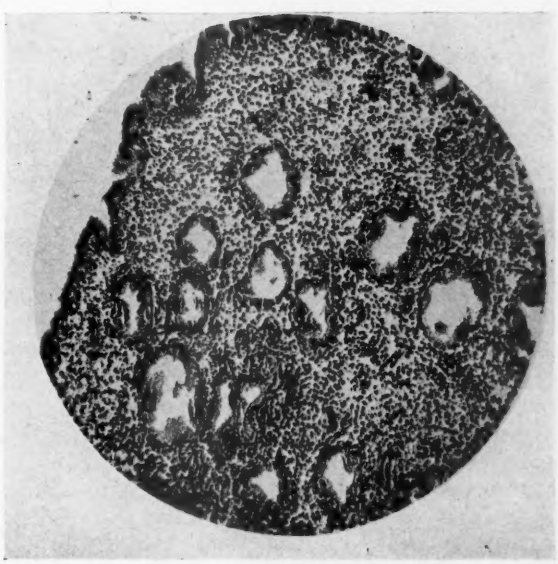


B.

Fig. 1.—Case 2. R. H. (*A*) Previous periods every six to eight weeks for ten days. Now bleeding for three weeks from a proliferative endometrium. (*B*) 350 mg. of pregneninolone given in seven days stopped bleeding. Biopsy on eighth day showed full progestational response of the endometrium.

CASE 2.—(Fig. 1.) R. H., 18-year-old white girl, had had irregular periods since her menarche at the age of 13 years. Periods occurred every six to eight weeks for ten days. Genitals were normal. Bleeding had been present for three weeks. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone 18 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Patient received 50 mg. of pregneninolone daily over a period of seven days, totaling 350 mg. Biopsy on the eighth day showed full progestational response of the endometrium. Regular menstrual cycles were established through a period of four months with 240 mg. pregneninolone given during the second half of the cycle.

CASE 3.—M. W., virgin, 14-year-old white girl, began to menstruate at 12 years of age. The periods were regular in the beginning, occurring every 24 days and lasting for five or six days. For the last three months, periods lasted two weeks followed by staining for one week. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. No biopsy was taken.

Therapy: Patient received a total of 250 mg. of pregneninolone in daily doses of 50 mg. For the following five months a menstrual cycle of twenty-six days could be established with 260 mg. of pregneninolone given in divided doses during the second half of the cycle, the bleeding lasting for four days.

CASE 4.—L. S., 15-year-old white girl, virgin; menses started at 12 years of age, occurring every 28 days and lasting for four or five days for one year, then amenorrheic for two years. She started to bleed profusely for two weeks. She was very anemic. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 18 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Received daily 50 mg. of pregneninolone for seven days, totaling 350 mg. Bleeding stopped after five days. During the following six months menstrual cycle occurred every thirty-five days and lasted four days without any further medication.

CASE 5.—G. L., 18-year-old white girl. Periods had occurred every twenty-eight days, lasted five to six days, and were regular, but for the last year they occurred every two months and lasted for two weeks. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a proliferative endometrium.

Therapy: Three hundred milligrams of pregneninolone were given for six days, daily dose 50 mg. The endometrial biopsy (taken eight days after therapy was started) showed some degree of progestational alteration. Bleeding stopped on the seventh day. Following this, patient received 260 mg. of pregneninolone during second half of cycle, whereby, for the last seven months a cycle of twenty-nine days was established.

CASE 6.—F. S., 18-year-old colored girl. The onset of the menstrual period occurred at eleven years of age. Periods had been regular, occurring every twenty-eight days, lasting four or five days. For last half year, periods had been irregular, every four or five weeks, lasting three weeks. Genitals were normal. Hormone determination: Estrogenic hormone 20 R.U. per day. Follicle-stimulating hormone nega-

tive. The endometrial biopsy showed a cystic and glandular hyperplasia.

Therapy: Patient received 350 mg. of pregneninolone in divided doses over a period of seven days. Bleeding stopped on the sixth day. The endometrial biopsy showed, on the twelfth day, a proliferative endometrium. With 260 mg. of pregneninolone a menstrual cycle of five weeks could be established.

CASE 7.—M. SP., 17-year-old white virgin. Menstrual periods began at fifteen years of age, occurring every thirty-six to forty days and lasting three days. For last four months periods occurred every twenty-three days, lasting twelve days. Rectal examination: No pathology. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. No biopsy.

Therapy: Patient received 300 mg. of pregneninolone in divided doses for six days. Bleeding stopped on the fourth day. Normal cycle has continued for three months without therapy. Regular.

CASE 8.—R. W., 14-year-old white virgin. Her first period was a continuous bleeding for six weeks. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 14 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Patient received 350 mg. of pregneninolone in divided doses over a period of seven days. Bleeding stopped on the fifth day. She had her second regular period with 240 mg. of pregneninolone given during second half of cycle.

CASE 9.—M. W., 17-year-old white virgin. First period started when patient was 16 years; then complete amenorrhea until four weeks ago when she started to menstruate which has continued until present time. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 20 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Patient received 350 mg. of pregneninolone in divided doses over a period of seven days. Oral therapy did not influence bleeding and on account of severe anemia (hemoglobin 40 per cent) corpus luteum hormone total of 40 mg. in 2 doses was given by injection, which stopped bleeding in seventy-two hours. Further menstrual periods could be obtained with oral pregneninolone medication, 350 mg. during the second half of cycle.

CASE 10.—J. St., 13-year-old white virgin. First menstrual period started three weeks ago, and patient is still bleeding. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Patient received 100 mg. of pregneninolone daily over a period of three days without any effect on the bleeding. General condition poor. (Hemoglobin 45 per cent.) She received 50 mg. of corpus luteum hormone by injection which stopped bleeding after last injection. Five normal periods were established since then by oral pregneninolone therapy, 350 mg. during second half of cycle.

CASE 11.—L. B., 15-year-old colored virgin. The onset of menstrual periods occurred at 13 years of age. She had two normal periods and became amenorrheic for twenty-one months. Patient is bleeding now for

six weeks. Rectal examination: No pathology. Hormone determination: Estrogenic hormone 16 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Patient received 350 mg. of pregneninolone in divided doses over a period of seven days. Bleeding did not stop and was allowed to continue for four days. Twenty-five milligrams of corpus luteum hormone were given by injection which stopped bleeding after forty-eight hours. Since then 6 normal periods could be established with 350 mg. of pregneninolone given during the second half of the cycle.

Maturity Bleeding.—

CASE 12.—D. E., 28-year-old white patient, had been married eight years and had never become pregnant. Onset of period occurred at fourteen years of age, and recurred every twenty-eight days, lasting four or five days. Periods were completely irregular for three years, alternating between amenorrhea and profuse bleeding. She has been bleeding for six weeks. Genitals: No pathology. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

Therapy: Patient received 350 mg. of pregneninolone in divided doses over a period of seven days. Bleeding stopped on sixth day. Endometrial biopsy ten days later showed some progestational alteration. Normal cycles for four months could be maintained with 260 mg. given in the second half of the cycle. Biopsies revealed that bleeding occurred from a very early secretory endometrium.

CASE 13.—A. G., 24-year-old white patient. The onset of the menstrual period began at 13 years of age, occurred every thirty-two days and lasted four or five days. For the last four months patient had bled for ten days followed by staining for twelve days. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

Therapy: Patient received for seven days 50 mg. of pregneninolone, totaling 350 mg. Biopsy on the tenth day revealed a proliferative endometrium. For the next three months, patient received 200 mg. orally in the second half of the cycle. Biopsies revealed some degree of progestational alteration.

CASE 14.—F. H., 35-year-old white patient. The menstrual period began at fourteen years of age, occurred every twenty-eight days, and lasted four or five days. Since her last pregnancy, starting with the first period, 6 weeks post partum, patient bled continuously for seven weeks. Genitals were normal. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

Therapy: Patient received 280 mg. of pregneninolone over a period of seven days in daily doses of 40 mg. Bleeding stopped on fifth day. Biopsy on ninth day revealed a proliferative endometrium. For the last four months a thirty-two-day normal menstrual cycle could be maintained with 280 mg. of pregneninolone. Biopsies taken premenstrually showed an early secretory endometrium.

CASE 15.—L. C., 32-year-old white patient. The menstrual period began at age of fourteen years, occurred every twenty-six to twenty-eight days, and lasted five days. She had spontaneous deliveries in 1932 and 1939. Following the last delivery in 1940, she had two normal periods, twenty-eight days apart. Her third period post-partum lasted for three weeks. The endometrial biopsy showed a cystic and glandular hyperplasia. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Fifty milligrams of pregneninolone were given daily for seven days, totaling 350 mg. Bleeding stopped after six days of therapy. Biopsy taken on the tenth day showed a proliferative endometrium. A twenty-eight-day cycle could be obtained for four months with 240 mg. of pregneninolone given in the second half of the cycle. Biopsies taken premenstrually showed some progestational alteration.

CASE 16.—E. L., 24-year-old colored patient. Onset of period occurred at twelve years of age. Period from the beginning was irregular. She was amenorrheic up to six months. Since patient was married, four years ago, periods have occurred every thirty-two to thirty-six days, lasting five days. She has never been pregnant. For last half year, menstrual bleeding has occurred for twelve days followed by staining for another 14 days. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone negative. Follicle-stimulating hormone was negative.

Therapy: Fifty milligrams of pregneninolone were given for six days, totaling 300 mg. Bleeding stopped after five days. Biopsy taken on the eighth day showed early progestational phase. Endometrial biopsies taken premenstrually for six months showed full progestational development.

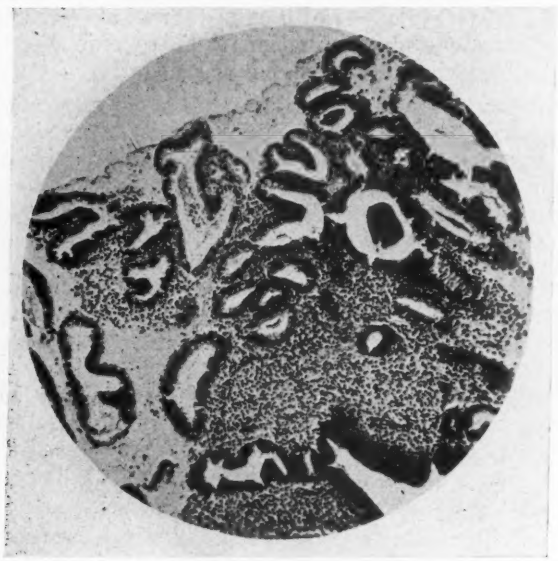
CASE 17.—B. W., 26-year-old white patient. The menstrual period began at the age of thirteen, occurred every twenty-eight days and lasted four or five days. She menstruated regularly until she had a child early in 1940. The first menstrual period after the delivery lasted for two weeks, with profuse bleeding; then she menstruated every eighteen days for two weeks. The endometrial biopsy showed an early secretory endometrium. Hormone determination: Estrogenic hormone 18 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Forty milligrams of pregneninolone were given for a period of seven days, totaling 280 mg. Bleeding stopped on the ninth day. Biopsy taken on the twelfth day showed a secretory endometrium. With a monthly dose of 250 mg. of pregneninolone a regular 30-day cycle could be established for the following 5 months. Several premenstrual biopsies taken showed a secretory endometrium.

CASE 18.—(Fig. 2.) H. G., 23-year-old white girl. The menstrual period began at fifteen years of age, occurred every thirty-two days, and lasted for five or six days. For one year, menstrual periods occurred every eight weeks; actual bleeding for three weeks. The endometrial biopsy showed a proliferative endometrium. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative.

Therapy: Fifty milligrams of pregneninolone were given for seven days, totaling 350 mg. Bleeding stopped on the tenth day. Biopsy

taken on the fourteenth day showed a secretory endometrium. She had regular periods every thirty-two days for seven days for the last five months, with 280 mg. of pregneninolone given during the second half of cycle. Several premenstrual biopsies revealed secretory endometrium.



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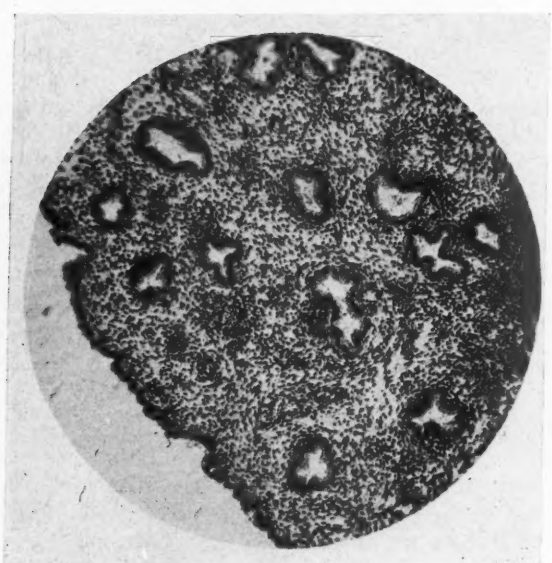

B.

Fig. 2.—Case 18. H. G. (*A*) The menstrual periods began at 15 years of age, occurred every thirty-two days and lasted for five or six days. For one year menstrual period every eight weeks; actual bleeding for three weeks. Now bleeding from a proliferative endometrium. Three hundred and fifty milligrams of pregneninolone in seven days stopped bleeding on tenth day. (*B*) Biopsy on fourteenth day showed secretory endometrium.

CASE 19.—M. B., 32-year-old white girl. The menstrual period began at 15 years of age, occurred every twenty-three days, and lasted for four days. Her first 3 periods after her last delivery lasted for two weeks. Patient has been bleeding profusely for three weeks. Genitals were normal. Hormone determination: Estrogenic hormone 8 R.U. per day. Follicle-stimulating hormone was negative. The endometrial biopsy showed a cystic and glandular hyperplasia.

Therapy: Patient received 350 mg. of pregneninolone over a period of seven days in daily doses of 50 mg. Bleeding stopped on the tenth day. Biopsy on the twelfth day revealed a proliferative endometrium. For the last six months a normal menstrual cycle could be maintained with 220 mg. of pregneninolone. Biopsies taken premenstrually showed an early secretory endometrium.

CASE 20.—L. R., 20-year-old white girl. Her menstrual period began at 14 years, occurred every twenty-six days, and lasted for four or five days. For the last two years, periods occurred every five or six weeks; she has been bleeding continuously for seven weeks. Genitals were normal. Hormone determination: Estrogenic hormone 16 R.U. per day. Follicle-stimulating hormone was negative. The endometrial biopsy showed a proliferative endometrium.

Therapy: Fifty milligrams of pregneninolone for a period of seven days; totaling 350 mg. Bleeding stopped on the twelfth day. Biopsy taken on the thirteenth day showed an early secretory endometrium. With a monthly dose of 240 mg. of pregneninolone a regular twenty-eight-day cycle could be established for the last four months. Several premenstrual biopsies showed a secretory endometrium.

COMMENT

Pregneninolone was very well tolerated by all our patients. The highest daily dose was 50 mg., totaling up to 350 mg. over a period of seven days; only one patient received 100 mg. daily for three days, totaling up to 300 mg. In 13 cases endometrial biopsies were obtained. The first biopsy was always taken before treatment was started, the second biopsy after therapy was effective and further biopsies for several months always from three to five days premenstrually. Biopsies taken before treatment was started showed in 6 cases proliferative endometrium, in 6 cases cystic and glandular hyperplasia, and in one case early secretory endometrium. Biopsies taken from eight to fourteen days after treatment had started, showed in 5 cases some degree of progestational endometrium, in 3 cases a generalized progestational response of the endometrium and in 5 cases a proliferative endometrium. Three cases of juvenile bleeding did not respond to oral therapy and received from 25 to 50 I.U. corpus luteum hormone by injection, which stopped bleeding from 48 to 72 hours after the injections were given. Regular menstrual cycles could be established with reduced medication, 200 to 240 mg. when given orally in the second half of the cycle.

CONCLUSIONS

1. Functional uterine bleeding may be due to a relationship between hormones and structural changes in the endometrial vascular supply.

2. The bleeding factors seem to be vascular within the endometrium and not dependent upon the histologic type of the endometrium.

3. Functional uterine bleeding can be controlled by oral use of pregneninolone, the effective dose ranging between 280 and 350 mg. given in daily doses of 50 mg.

4. From 6 to 7 times the amount of pregneninolone by weight is required orally as compared with progesterone when given by injection.

5. Three patients with juvenile bleeding did not respond to oral therapy and received from 25 to 50 I.U. of corpus luteum hormone by injection, which stopped the bleeding in from 48 to 72 hours.

6. Two cases showed complete progestational changes of the endometrium.

7. Normal menstrual cycle can be maintained with smaller doses (200 to 240 mg.) when given in the second half of the cycle.

8. Further studies are necessary to evaluate the minimum dosage for controlling the bleeding and the maintenance of a regular menstrual cycle.

I am indebted to Dr. Benjamin P. Watson, Director, Department of Obstetrics and Gynecology, Sloane Hospital for Women, for constant encouragement and advice, and for his placing the material of the Sloane Hospital for Women and the Vanderbilt Clinic at my disposal.

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Macknight, Ella: Almost Complete Occlusion of the Vaginal Orifice Following Childbirth, Med. J. Australia **2:** 699, 1940.

The author reports a case of almost complete occlusion of the introitus due to formation of a septum by adhesions of both labia minora. The septum varied between one-fourth and one-half inch in thickness. It developed after the birth of a premature (8 mo.) baby eighteen months previously. Coitus was impossible, but menstruation had been normal. There was no difficulty with micturition.

William Berman

UTERINE CONTRACTIONS IN DYSMENORRHEA

WILLIAM BICKERS, M.D., RICHMOND, VA.

SEVERE, intermittent, cramplike pain associated with the menses is the most common cause of disability among young women. An eastern college for women reports 10 per cent of its absentee days as caused by painful menstruation. The Medical Department of one of our large industries reports that dysmenorrhea costs its company $20,000 annually.

The clinical picture is well known to every practitioner. A young woman, usually under twenty-five years of age, comes to the doctor's office seeking his scientific advice for the alleviation of a condition which numerous highly advertised proprietary drugs have failed to relieve. She gives a history of acute, spasmodic pain with the menses which usually dates from puberty. Pelvic examination reveals no pathology. This is the primary type of dysmenorrhea. There is a second group, small in number, and usually in the fourth decade of life, who have fibroids, endometriosis, pelvic inflammatory disease, uterine polyp, or some other pathology to explain the acquired dysmenorrhea. This is the secondary type. The first and more important group has a physiologic dysfunction toward which this study is directed. The effect of several commonly used drugs upon this abnormal physiology is also investigated.

PATHOLOGIC PHYSIOLOGY

The pain of dysmenorrhea arises from the intermittent contractions of the myometrium. Normal contractions of muscle fibers produce no pain; while in the absence of adequate blood supply, these contractions become acutely painful. It cannot be demonstrated that the dysmenorrheic uterus is any less well supplied with blood than the nonpainful menstruating uterus. However, this study does demonstrate the presence of tetany in dysmenorrhea as contrasted with the atony seen in the nonpainful menstrual contractions. This tetany may interfere with normal oxygenation of the myometrium. The high contractions normally present during menstruation may then cause pain. The pathologic physiology may be comparable to that of angina pectoris and that which occurs when the muscles of the forearm are exercised after a tourniquet has been applied.[3]

It has been shown in previous studies that uterine contractions during menstruation in a normal ovulatory cycle are characterized by relatively high amplitude, low frequency, and marked absence of tetany. The absence of tetany permits the uterus to relax between contractions, thus improving its blood supply and the contractions are painless. High amplitude contractions produce no pain, provided there is adequate relaxation. Conversely, there is no pain associated with tetany

unless there is superimposed upon it the high contractions of corpus luteum influence. One may conclude, therefore, that two conditions are usually present in primary dysmenorrhea; namely, tetany plus high amplitude contractions.

TECHNICAL PROCEDURE

Fifteen patients who suffered severely with each menses and in whom no pelvic pathology could be demonstrated were chosen for this study. Their ages varied from sixteen to twenty-six; the average age was twenty-one. Nine were nulliparas. Nine were married and 4 were

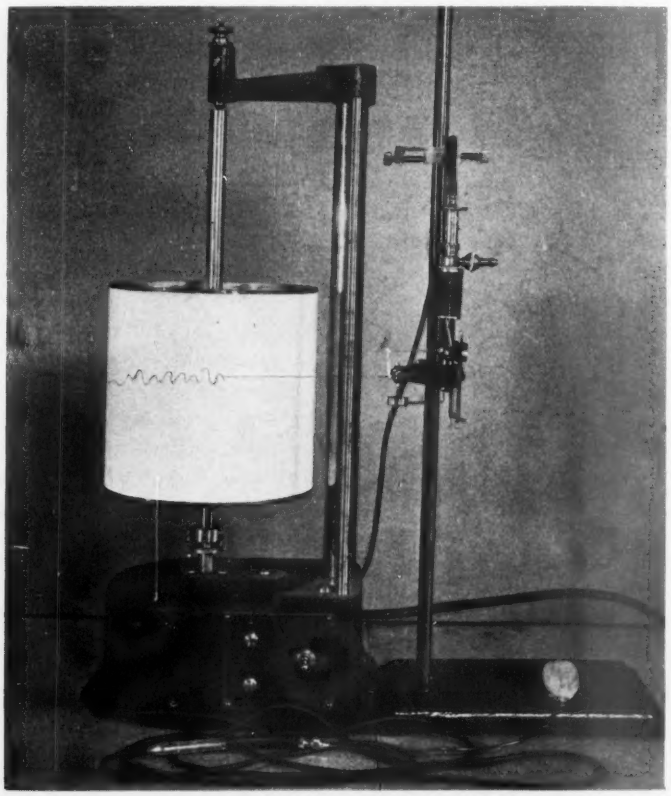

Fig. 1.—The distended balloon connected through a closed water system to the mechanical ink recorder. The electric kymograph is equipped with a timer.

virgins. All of the patients menstruated on cycles from twenty-four to thirty-two days. Their cooperation was obtained by explaining to them that the procedure was an attempt to find the cause of their dysmenorrhea.

A small condom balloon attached to a flexible metal cannula was placed in the uterine cavity after dilating the cervix with a very small uterine sound. This may be accomplished with a minimum amount of discomfort to the patient. The cannula is connected by a rubber tube to a mechanical ink writer which responds through a delicate system of levers to small variations in the intrauterine pressure. The system is filled with water which transmits directly the pressure changes in the

balloon to the mechanical recorder. This has been found to be more efficient than air, because the compressibility of air may introduce some error. The writing point connected to the mechanical recorder writes the tracings of uterine contractions upon a revolving kymograph (Fig. 1).

At least two tracings were made on each patient, one during the late luteal or premenstrual phase and the other while the patient was actually menstruating and experiencing her dysmenorrhea. The tracings were permitted to run for at least thirty minutes. When a drug was administered, adequate time was allowed to observe its effect. Objections to this technique have been raised on the grounds that a foreign body distending the uterus would alter the normal patterns of uterine motility.

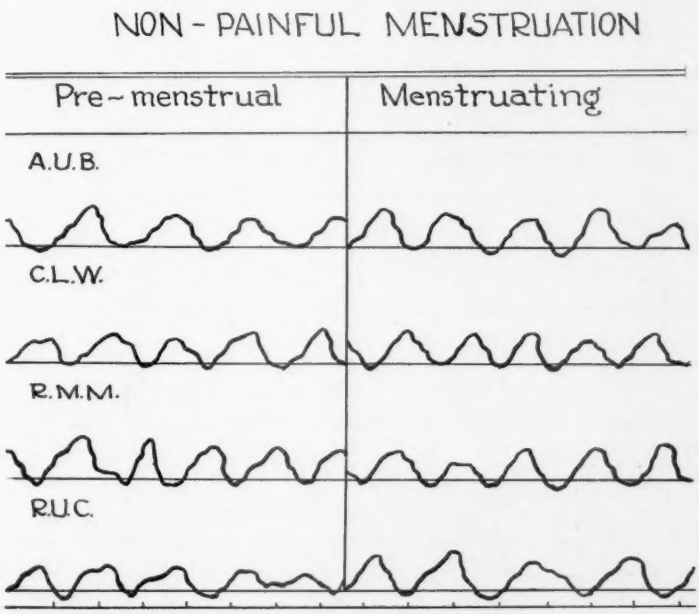

Fig. 2.—The premenstrual contractions have a relatively high amplitude. Each contraction returns to the base line, showing the absence of tetany. The menstruating contractions are similar and painless.

Considerable experience has shown that the tracings give an accurate picture of uterine contractility for the time of the cycle at which they are taken. The results on the same case at different phases of the cycle, and also in different patients are comparable when the technical procedure is the same in all experiments. Furthermore, the intrinsic pattern of motility is always brought out and cannot be altered by variations in pressure. For this study, the pressure in the system was kept between 30 and 50 mm. of mercury, so that the tracings could be fairly compared.

MOTILITY IN NONPAINFUL MENSTRUATION

A number of patients with normal, nonpainful menstruation have been studied. The pattern of uterine motility in these cases has been previously reported.[1] During the follicular phase (pre-ovulatory), the con-

tractions are low in amplitude, rapid, and somewhat tetanic (Fig. 2). These contractions are characteristic of unopposed estrogen influence. During the luteal phase (postovulatory), the contractions assume a much higher amplitude, lower frequency, and tetany is abolished. This is the progesterone influence. Seven tracings were taken in this group while the patient was menstruating. These nonpainful menstrual contractions show a complete absence of tetany. With this type of motility during menstruation, no pain is experienced (Fig. 2). The writing point returns to the base line after each contraction, showing complete relaxation of the uterus. These patterns of uterine motility have now been observed by several investigators. They are consistent and may be accepted as the true picture of uterine contractility in the normal ovulatory cycle.

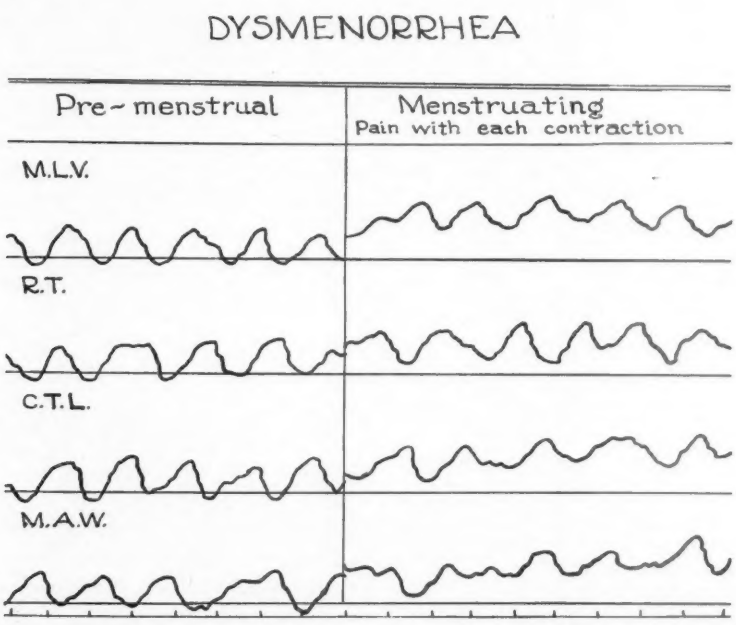

Fig. 3.—The premenstrual contractions have a relatively high amplitude, each contraction returns to the base line, and there is no tetany. The menstruating contractions are similar except they do not return to the base line because the uterus is tetanic.

MOTILITY IN PAINFUL MENSTRUATION

In each of the 15 cases studied, a normal ovulatory cycle was found. The presence of a corpus luteum was evidenced by the high amplitude, low frequency contractions seen only when the uterus is under progesterone influence. The presence of a corpus luteum was further demonstrated by finding a secretory endometrium during the premenstrual phase in all cases. Tracings taken during the premenstrual phase on these patients with dysmenorrhea showed the usual high amplitude, low frequency, atonic type of contraction (Fig. 3). However, the tracings which were taken during menstruation on these cases, usually on the first day and while the patient was experiencing her most severe

pain, showed a marked degree of tetany with the usual high amplitude contractions superimposed upon it (Fig. 3). This must be the typical pattern of uterine motility in dysmenorrhea because it was present in 13 of the 15 cases studied. Tetany was never seen in the nonpainful menstrual contractions. Contractions are similar in both groups, except for the tetany in the latter. In this group, not a single contraction ever returned to the base line, while in the nonpainful group all contractions returned either to the base line or below it. For the two patients who experienced typical dysmenorrhea, but who had a normal atonic type of contraction, there is no satisfactory explanation.

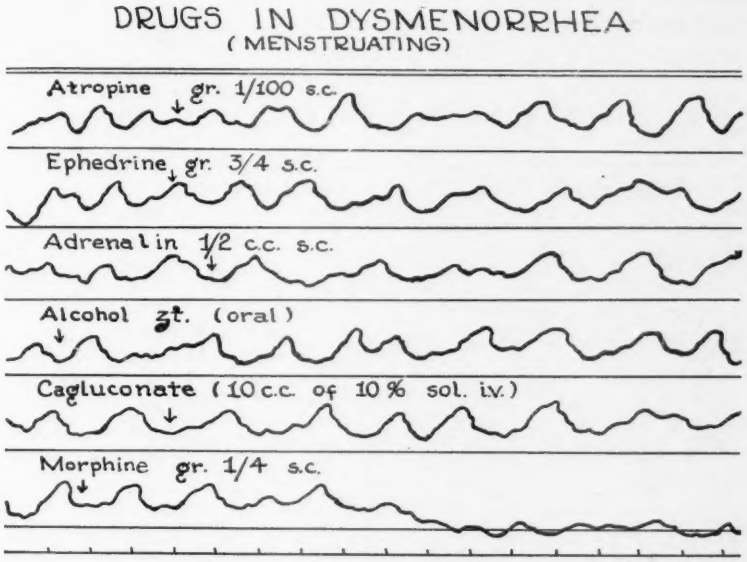

Fig. 4.—Atropine, ephedrine, adrenalin, alcohol, and calcium gluconate do not alter the contractions. Morphine abolishes tetany and diminishes the amplitude of each contraction.

EFFECT OF DRUGS ON MOTILITY IN PAINFUL MENSTRUATION

1. *Atropine.*—This drug has been frequently used on the theory that uterine cramps result from parasympathetic nerve stimulation. Atropine inhibits the parasympathetic nerve endings and thus should inhibit the contractions. Tracings were taken on three menstruating uteri after 1/100 gr. of atropine sulfate, subcutaneously had been given. No effect upon uterine motility could be demonstrated and there was no relief from pain (Fig. 4).

2. *Ephedrine.*—Two patients received ephedrine sulfate, ¾ gr. t.i.d., for two days prior to the menses and on the first day of menstruation when the tracing was taken. Contractions were not altered in amplitude or frequency, nor was there any diminution of tetany. Pain was not relieved (Fig. 4).

3. *Adrenalin.*—On the assumption that sympathicomimetic drugs inhibit uterine contractions, the use of adrenalin has been advocated in dysmenorrhea. The effect of ½ c.c. (1-1000) subcutaneously in four patients was studied. Some diminution in tetany was observed, the

amplitude of contractions continued to be high, but did not return to the base line. Pain was not relieved (Fig. 4).

4. *Morphine.*—It is well known that morphine relieves the pain of dysmenorrhea. To determine whether this was only an effect upon the central nervous system, or whether it actually inhibited uterine contractions, ¼ gr. of morphine was given subcutaneously to four patients. Within ten minutes the amplitude and rate of contractions were diminished, tetany abolished, and pain relieved (Fig. 4).

5. *Alcohol.*—Whiskey is a time-honored remedy for menstrual cramps. Two ounces of whiskey were given to each of three patients, all of whom said their pain was much relieved within thirty minutes. Tracings taken after thirty minutes showed no effect upon amplitude, rate, or tetany. Perhaps the vasodilating effect of alcohol may improve the relative ischemia of the myometrium (Fig. 4).

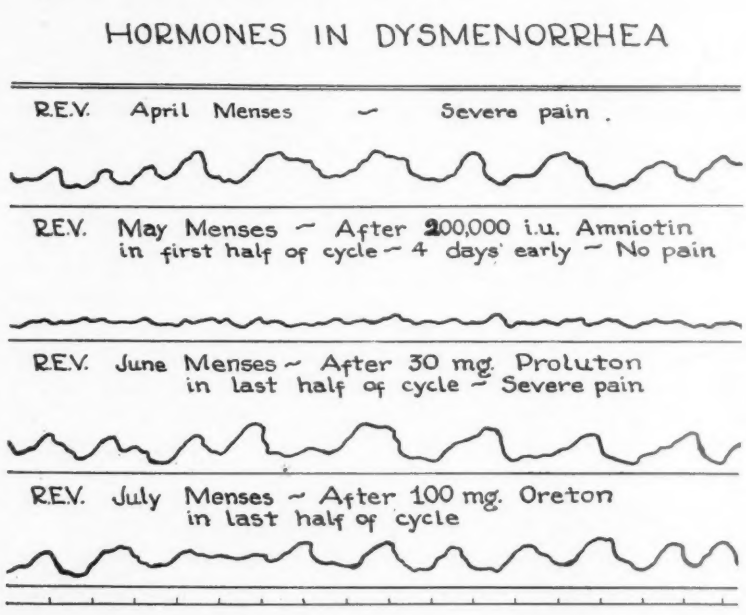
HORMONES IN DYSMENORRHEA
R.E.V. April Menses ~ Severe pain .
R.E.V. May Menses ~ After 200,000 i.u. Amniotin in first half of cycle ~ 4 days early ~ No pain
R.E.V. June Menses ~ After 30 mg. Proluton in last half of cycle ~ Severe pain
R.E.V. July Menses ~ After 100 mg. Oreton in last half of cycle

Fig. 5.—Estrogen in the form of amniotin prevented ovulation, and the menstrual contractions are low in amplitude because progesterone is absent. Progesterone in the form of proluton and testosterone in the form of oreton do not affect the pattern of uterine contractions.

6. *Calcium Gluconate.*—Ten cubic centimeters of 10 per cent solution of calcium gluconate were injected intravenously into one patient. There was no effect upon amplitude, rate, or tetany, and no relief from pain (Fig. 4).

EFFECT OF HORMONES ON MOTILITY IN PAINFUL MENSTRUATION

1. *Estrogen.*—It has been observed by other investigators and confirmed by this study that dysmenorrhea occurs only with the high amplitude contractions of progesterone influence. Painful menstruation does not occur in the anovulatory cycle. Large amounts of estrogen given during the first half of the cycle inhibit the gonadotropic hormone of the anterior pituitary to the point where follicle rupture and luteiniza-

tion are prevented. In those cases where ovulation is not prevented, the luteinizing gonadotropin may be inhibited to the point where progesterone influence will be minimized and uterine contractions will have a lower amplitude. Two patients were each given 200,000 I.U. of estrogen (amniotin) in the follicular phase of the cycle. Ovulation did not occur as evidenced by the persistent proliferative endometrium, and the tracings during menstruation showed the low amplitude, high frequency type characteristic of estrogen dominance. In the absence of high amplitude contractions, no pain was experienced (Fig. 5).

2. *Progesterone.*—Since Reynolds reported the inhibitory action of progesterone on the myometrium, this hormone has appeared to provide logical therapy for dysmenorrhea.[2] It has already been shown, however, that this hormone is responsible for the high amplitude contractions which are always present in the luteal phase of the cycle. In nonpainful menstruation, progesterone also abolishes the tetany caused by estrogen. This tetany recurs in the dysmenorrheic tracings and the logical therapy, therefore, would seem to be the artificial administration of the hormone. Two patients each received 30 mg. of synthetic progesterone in the latter half of their cycle. High amplitude contractions persisted, there was no diminution of tetany, and no relief from pain. This observation increases our confusion regarding hormone therapy in general. I do not know why progesterone will inhibit uterine motility in vitro and apparently increases the force of uterine contractions in vivo. Why does progesterone abolish tetany in vitro, but in relatively large doses apparently does not affect it in vivo? Our increasing knowledge of the metabolism of progesterone may soon explain this apparent inconsistency (Fig. 5).

3. *Testosterone.*—This hormone is said to have a direct inhibitory influence upon the myometrium. One hundred miligrams of testosterone propionate were given to one patient during the latter half of her cycle. The tracing shows no effect upon the amplitude, rate, or tetany. Pain was not relieved (Fig. 5).

COMMENT

Rational therapy for dysmenorrhea must be directed toward the pathologic physiology of the uterine contractions. To say that the pain is psychogenic, or that certain individuals have a low threshold adds nothing to our knowledge of the condition. Furthermore, it is true that the contractions during painful menstruation have a tetany not present in the normal group. Wilson and Kurzrok have recently reported a similar study in which they conclude that the uterine contractions in dysmenorrhea are not different from those seen in the normally menstruating uterus.[2] With this conclusion I cannot concur. In 13 of my 15 patients, a marked degree of tetany was observed with superimposed high amplitude contractions. In the nonpainful menstruating uterus, the high amplitude, luteal type of contractions is always seen, but never associated with tetany. The question which will immediately come to the mind of an investigator in this field is how one can determine the base line from which to measure the degree of tetany. Most uteri become spastic upon introduction of the balloon, but this artificially induced tetany relaxes after several minutes. All of the tracings in this study

were done at least fifteen minutes after the introduction of the balloon. In all cases morphine, gr. ¼, was given at the end of the experiment, fifteen minutes allowed to elapse, and the tracing again taken. This was done in order to establish the base line for each uterus. In the 7 cases of nonpainful menstruation, the relaxing effect of morphine did not greatly alter the base line to which each contraction returned. However, in the dysmenorrheic uteri the writing point dropped from ½ to 1½ cm. below the lowest point of uterine contraction after giving ¼ gr. of morphine (Fig. 4). This demonstrates rather conclusively that the dysmenorrheic uterus is a tetanic uterus.

SUMMARY

1. Dysmenorrhea occurs in the presence of high amplitude contractions superimposed upon tetany.

2. High amplitude contractions occur only in the presence of a corpus luteum. It follows therefore, that dysmenorrhea occurs only in the ovulatory cycle.

3. Atropine, ephedrine, adrenalin, and calcium gluconate do not alter uterine motility in dysmenorrhea and give no pain relief.

4. Alcohol does not alter uterine motility, but appears to diminish the pain through its effect either upon the nervous system or by its vasodilating effect upon the arterioles of the myometrium.

5. Morphine diminishes the amplitude of the contractions, abolishes tetany, and relieves the pain.

6. Estrogen in the first half of the cycle in large doses may either prevent ovulation or inhibit the luteinizing hormone of the anterior pituitary, thereby curtailing the progesterone effect on the uterus. Since high amplitude contractions occur only with progesterone, these are eliminated and pain relieved.

7. Progesterone administered subcutaneously does not change the contractions during menstruation in the ovulatory cycle and gives no pain relief.

8. Testosterone has no effect upon the menstrual contractions in the ovulatory cycle and gives no pain relief.

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807 WEST FRANKLIN STREET

Rau, R. K., Aiyar, A. A., and Mathew, T. V.: Quintuplets. A Record of a Premature Delivery, Brit. M. J. 1: 127, 1940.

A case of monozygotic quintuplets is reported. The fetuses were expelled during the sixth month of gestation and were attached by five separate umbilical cords to a single placenta which revealed one chorion and five amniotic sacs.

The infants, which averaged 14.0 cm. crown-rump length, died a few minutes after birth.

FRED L. ADAIR AND RAY YOUNG

POSTABORTAL TETANUS

A Review of the Literature, and a Report of 14 Additional Cases

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POSTABORTAL tetanus as an entity has been well established by the work of Chantemesse and Widal,[1] Heyse,[2] Rubeska,[3] and others,[4, 5, 43, 45] who were able to isolate the causative organism from uterine discharges. It is of infrequent occurrence and has occasioned but minor notice in even such an excellent work as Taussig.[42]

In 1898, at the Congress of Gynecology and Obstetrics at Marseilles, Sepet[5] reported 125 cases of puerperal tetanus (48 postabortal). Schneider[4] was able to collect only 109 cases from the literature, to which he added two of his own (1925). While those who refer to the previous literature at all, cite Schneider's series, there are scant references to Sepet's splendid report. Schneider's survey focused attention upon postabortal tetanus, and his paper was followed by the reports of Auvray,[6] Houel, Lesini and Morand,[7] Chalier and Rousset,[8] Byrne,[9] Hebold,[10] Mattson and Starkey,[11] Laffont, Ezes, and Mereaur,[12] Martinez,[13] Arnaudet,[14] Sicard,[15] Duvoir and associates,[16] Valenti,[17] Janbon and associates,[18] Bernardbeig,[19] Warembourg and associates,[20] Kernbach and Dachnovici,[21] de Rougemont and Clavel,[22] Rossi,[23] and Petersen.[24] More recently cases have been reported by Komaromy,[25] Harteman,[26] Desbonnets,[27] Breborowicz,[28] Blondin,[29] Turries and associates,[30] Ferron and Torlet,[31] Menendez,[32] Ximeno,[33] de Barros,[34] Goyer and Bernard,[35] and Goyer[36] and more recently that of Bush[37] (see Table I). It is interesting to note that of these only four reports[9, 11, 25, 37] have appeared in English. The majority of the reports have originated on the continent, and are chiefly French and German. One notes with interest that no collected series has appeared from India, where Knight[38] has indicated conditions for the occurrence of post-partum tetanus would seem to be ideal.

We became interested in postabortal tetanus by the recent occurrence in and recovery of a patient (Case 6) on the Tulane Gynecological Service at Charity Hospital and were able to collect 13 additional cases from the services at Touro Infirmary and Charity Hospital. We feel that such a large local series tends to show that the condition is probably more common than the literature indicates.

CASE REPORTS

Case 1.—C. H. (No. S363), married, negress, 22 years of age, was admitted to the emergency room on Mar. 14, 1926 at 4:50 P.M., in convulsions. A history of criminal abortion ten days previously, and physical

TABLE I

AUTHOR	NO. OF CASES	NO. RECOVERED	MORTALITY %
Schneider[4]	111	10	91
Auvray[6]	2	2	100
Houel and others[7]	2	0	100
Chalier and Rousset[8]	1	0	100
Byrne[9]	1	0	100
Hebold[10]	1	0	100
Mattson and Starkey[11]	1	1	0
Laffont and others[12]	1	0	100
Martinez[13]	1	1	0
Arnaudet[14]	1	0	100
Sicard[15]	2	1	50
Duvoir and others[16]	1	0	100
Valenti[17]	1	1	0
Janbon and others[18]	1	0	100
Bernardbeig[19]	1	0	100
Warembourg[20]	1	0	100
Kernbach and Dachnovici[21]	2	0	100
Rougemont and Clavel[22]	1	0	100
Rossi[23]	1	1	0
Petersen[24]	1	0	100
Komaromy[25]	1	0	100
Hartman[26]	1	0	100
Desbonnets[27]	1	0	100
Breborowicz[28]	2	0	100
Blondin[29]	2	0	100
Turries and others[30]	1	1	0
Ferron and Torlet[31]	1	0	100
Menendez[32]	1	0	100
Ximeno[33]	3	2	33
de Barros[34]	1	0	100
Goyer and Bernard[35]	2	1	50
Goyer[36]	1	1	0
Bush[37]	5	0	100
This series	14	6	57
Collected literature Total cases	170	28	84

findings compatible with tetanus were obtained. A diagnosis of tetanus was made in the admitting room. Patient died fifteen minutes after admission. 20,000 units antitetanic serum, intramuscularly, and 20,000 units intravenously were administered by the admitting physician. Sodium bromide and chloral hydrate were used for sedation. Autopsy was performed by the coroner.

CASE 2.—C. H. (No. G12005), married, negress, 34 years, was admitted on May 16, 1929, at 11:10 P.M., with a history of an abortion eight days prior to admission. On admission she had an elevated temperature, rigid neck, and the abdominal musculature was tense. Spinal fluid pressure was normal. Examination of fluid presented no unusual findings. She received a total of 70,000 units of antitetanic serum intramuscularly, and 30,000 units of antitetanic serum intravenously. Sedations of morphine and chloratone were used. The patient seemed to improve markedly, her maximum temperature of 105° F. on the second day returned to normal by the third day. On the fifth day she developed pneumonia which continued progressively worse, and she died on the eleventh hospital day. Autopsy was performed by the coroner.

CASE 3.—C. H. (No. S455), married, negress, 22 years of age, was admitted on Sept. 6, 1931, eight days after having sustained a criminal abortion. She was admitted with a chief complaint of difficulty in eating and slight convulsions on stimulation. Day after admission her temperature rose to 102.2° F. and therefore gradually declined to normal. She received 40,000 units antitetanic serum intramuscularly on admission. During the next four days she received an additional total dose of 120,000 units of antitetanic serum intramuscularly. Chloral hydrate, sodium amytal, and chloratone were employed for sedation. Nutrition was maintained by tube feeding. She made an uneventful recovery and was discharged Oct. 1, 1931.

CASE 4.—C. H. (No. 774 S 461), unmarried negro school teacher, 23 years of age, gravida i, last menstrual period two months previously, had an abortion nine days before entering the hospital on Jan. 7, 1932 at 9:05 P.M. On admission she was unable to open the mouth, and had rigidity of neck muscles. Spinal fluid pressure was slightly increased. Other laboratory findings were negative. She was immediately given 7,500 units of antitetanic serum intraspinally. She received a total dosage of 5,500 units of antitetanic serum intramuscularly and 29,000 units intravenously. Sodium amytal and morphine were used as sedation. Nutrition was maintained by infusions and Levin tube feeding. Her temperature rose progressively to 105° F., pulse 136, respiration 34. She died on Jan. 10, 1932, at 9:55 A.M. At autopsy, necrotic placental rests were found in the uterine cornu. She also had a terminal bilateral bronchopneumonia.

CASE 5.—C. H (No. H38649 S 477), married, negress, 29 years of age, gravida vii, was admitted on Oct. 22, 1932, at 7:15 P.M. She gave a history of a spontaneous abortion eight days earlier at or about the seventh week of gestation. The chief complaint on admission was difficulty in swallowing. Laboratory findings were negative. She received a total dosage of 40,000 units of antitetanic serum intramuscularly, and 20,000 units intravenously. Chloral hydrate, bromides, avertin, and morphine were used as sedatives. She grew progressively worse, temperature gradually rose to a maximum of 106° F. just prior to death, which occurred on Oct. 28, 1932, at 7:30 A.M. Coroner performed autopsy with a report of tetanus and postabortal septicemia.

CASE 6.—A. G. (T No. L1256), married, white multigravida, was admitted on Mar. 2, 1934, with a history of a criminal abortion by a local midwife twelve days previously. She manifested her symptoms for the first time two days prior to admission. On admission she had an elevated temperature and trismus. Laboratory findings were negative. She received 30,000 units of antitetanic serum intrathecally and 30,000 units intravenously. Sodium amytal was used for sedation. Her nutrition was maintained by Levin tube. Due to hemorrhage a dilatation and curettage were done and a large quantity of infected products of pregnancy removed. Patient was discharged on Mar. 11, 1934, symptom free.

CASE 7.—Mrs. W. P. (T No. L6317), 17-year-old gravida iv, was admitted Oct. 5, 1934, with complaints of pain in the back and neck, trismus, and uterine bleeding. She gave a history of two criminal abortions, one two years ago, and the last ten days previous to admission.

Her symptoms began three days prior to admission. Laboratory reports were essentially negative except for a marked leucocytosis. She received a total of 110,000 units of antitetanic serum intravenously and 245 gr. of sodium amytal in dosages of 7½ gr. over a period of twenty days. Sedation was then maintained with bromides and chloral hydrate for a period of three days. She was discharged symptom free, Nov. 7, 1934.

CASE 8.—Mrs. M. M. (T., No. L7839), aged 21 years, housewife, was admitted Dec. 13, 1934, 1:40 P.M. with opisthotonus and trismus. Patient had a criminal abortion seven days before admission. She developed convulsions on the fifteenth and was given sodium amytal. This was repeated on the sixteenth and patient died at 8:55 P.M. She had also received chloral hydrate and sodium amytal in an attempt to control convulsions. Her temperature had mounted steadily from the admission temperature of 98° F. to a terminal temperature of 106.6° F.

CASE 9.—Mrs. S. M. N. (T., No. 38-72935, C. H.), white octigravida, aged 31 years, was admitted to the Gynecological service Sept. 10, 1938, presenting a history of an induced abortion fourteen days previously, and exhibiting the signs of tetanus; viz., risus sardonicus, stiff neck, increased biceps, and patellar reflexes. Muscular pains had begun one week prior to admission, growing progressively worse. Patient's husband was employed as a riding club instructor; and the patient stated that she had spent considerable time around horses. Her physician had given her 3,000 units of antitetanic serum intramuscularly. The cervical canal was dilated about 2 cm. The uterine discharge was foul. The conjunctival and intradermal tests for tetanus antitoxin proved negative; consequently, 50,000 units were administered intravenously. The cerebrospinal fluid pressure was found to be 10 mm. Hg, rising to 18 mm. as the result of application of pressure to the neck veins, and falling promptly to the original figure when the pressure was released. The fluid was crystal clear, and proved to be "negative" upon microscopic, chemical and cultural study. Twenty-seven cubic centimeters were permitted to escape drop by drop. An equivalent quantity of tetanus antitoxin (Gilliland, 80,000 American units) was introduced. During the subsequent days, a total of 280,000 units were administered. Of this amount 200,000 units were given intravenously.

Oral temperature was 102° F., with pulse rate of 100, respiratory rate of 25 at time of admittance. Maximum temperature was 102.2° F. (axilla) on the third hospital day. At that time pulse was 130 per minute; patient was afebrile after the sixth day. Nutrition was maintained by Levin tube feedings. Total of 41.25 gr. of sodium amytal were given intramuscularly. Patient was discharged Sept. 29, 1938.

CASE 10.—H. T. (C. H., No. 38-67750), 24-year-old, colored, gravida vi, complaining of "jerking in throat started by noise" and mild convulsive seizures on the day of admission. Patient had an abortion four days previously. She received 40,000 units antitetanic serum intramuscularly and 40,000 units intravenously. She was also given avertin. Nutrition was administered by Levin tube and infusions. She died on Sept. 27, 1938, at 5:18 P.M. Coroner reported postabortal tetanus.

CASE 11.—A. P. (C. H., No. 138-76076), 20-year-old unmarried negress, gravida i, was admitted to the hospital on Nov. 20, 1938. She stated that she had had "lockjaw for three days." Criminal abortion was

performed seven days previously. Laboratory findings were negative. She received 20,000 units of antitetanic serum intravenously, and 40,000 units intramuscularly; also avertin and sodium phenobarbital. Nutrition was given by infusion and Levin tube. She died Nov. 24, 1938. Coroner's report: postabortal tetanus.

CASE 12.—Mrs. E. B. (T., No. S 2784), 35 years, gravida ii, was admitted Mar. 26, 1940, with trismus and rigidity of neck. Patient gave a history of an abortion six days earlier and stated that the vagina had been packed by a midwife the day prior to admission. She received 160,000 units of antitetanic serum intravenously and 160,000 units intramuscularly. On March 27 she was given 120 gr. of sulfanilamide which was followed by cyanosis. She was also given seconal and morphine. Nutrition was given by infusion and stomach tube. Patient recovered uneventfully and was discharged on April 18, 1940.

CASE 13.—Mrs. S. R. (T., No. S 6838), 26 years, gravida i, was admitted with profuse uterine bleeding which she stated was an excessive flow but at her normal period. Two days after admission she had a convulsion after swallowing. A history was later obtained of criminal abortion fourteen days previous to admission. She received 80,000 units of antitetanus serum intravenously, and chloratone as a sedative. She developed a "trigger zone" in the pharynx and had a mild convulsion whenever she attempted to swallow. Her condition continued steadily worse, and she died Aug. 3, 1940, at 12:25 P.M. Autopsy was performed. Diagnosis: postabortal tetanus.

CASE 14.—Miss K. K. S. (T., No. S 4411), was admitted May 9, 1940, with bleeding and a history of criminal abortion performed the previous day. Laboratory findings were negative. She was afebrile and getting along very well until seven days after admission when she developed the classical signs of tetanus. She was given 80,000 units of antitetanus serum, intramuscularly and 40,000 units intravenously, 120 gr. of sulfanilamide, 30 c.c. of neoprontosil, a transfusion, morphine and sodium phenobarbital. She recovered and was discharged May 26, 1940.

DISCUSSION

Tetanus occurs more frequently after abortion than after full-term delivery. It occurs much more frequently after criminal than after spontaneous abortion. In this series, there was but one spontaneous abortion. The onset of symptoms occurs between the sixth and twelfth postabortal day, though occasionally symptoms have been reported earlier, in rare instances occurring immediately after the termination of pregnancy. Auvray and Frantz[43] state that the incubation period is much shorter, ranging between one and six days. In this series the earliest onset of symptoms was four days after abortion and the latest sixteen days (see Table II).

As DeLee[41] points out, "the pathology, symptoms, diagnosis and treatment do not differ from that of surgical tetanus." Often, in fact usually, the symptoms are those of classical tetanus. However, they are not infrequently atypical. There are instances reported where the only sign was a slight rigidity of the abdominal muscles, to be followed much later by the other signs of tetanus. Only three of our patients

TABLE II

CASE	RACE	AGE	GRAVIDA	INCUBATION PERIOD DAYS	TREATMENT*	OUTCOME
1	Colored	22	?	10	*A.T.S.* 20,000 units I.V. 20,000 units I.M. Sodium bromide Chloral hydrate	Died
2	Colored	34	?	8	*A.T.S.* 70,000 units I.M. 30,000 units I.V. Morphine Chloratone	Died
3	Colored	22	?	8	*A.T.S.* 160,000 units I.M. Chloral hydrate Sodium amytal	Recovered
4	Colored	23	i	9	*A.T.S.* 7,500 units intrathecally 5,500 units I.V. 29,000 units I.M. Sodium amytal Morphine	Died
5	Colored	29	vii	8	*A.T.S.* 40,000 units I.M. 20,000 units I.V. Chloral hydrate Bromide Avertin Morphine	Died
6	White	28	?	10	*A.T.S.* 30,000 units I.V. 30,000 units intrathecally Sodium amytal	Recovered
7	White	17	iv	10	*A.T.S.* 110,000 units I.V. Sodium amytal Bromides Chloral hydrate	Recovered
8	White	21	i	7	Chloral hydrate Sodium amytal	Died
9	White	31	viii	7	*A.T.S.* 250,000 units I.V. 160,000 units intrathecally Sodium amytal	Recovered
10	Colored	24	vi	4	*A.T.S.* 40,000 units I.M. 40,000 units I.V. Avertin	Died
11	Colored	20	i	7	*A.T.S.* 20,000 units I.V. 40,000 units I.M. Avertin Phenobarbital	Died

*A.T.S., Antitetanus serum; I.V., intravenously; I.M., intramuscularly.

TABLE II—CONT'D

CASE	RACE	AGE	GRAVIDA	INCUBATION PERIOD DAYS	TREATMENT*	OUTCOME
12	White	35	ii	6	*A.T.S.* 160,000 units I.V. 160,000 units I.M. Sulfanilamide Seconal Morphine	Recovered
13	White	26	i	16	*A.T.S.* 80,000 units I.V. Chloratone	Died
14	White	24	i	8	*A.T.S.* 80,000 units I.M. 40,000 units I.V. Sulfanilamide Neoprotosil Transfusions Morphine	Recovered

were admitted with actual "lockjaw." Since postabortal tetanus may develop para passu with puerperal septicemia or other complications, its symptomatology may be masked. This finding has repeatedly been reported.

All are agreed that adequate therapy is based on the following factors: (1) sedation, (2) adequate use of antitetanic serum, and (3) maintenance of nutrition. The combination of serum and sedation is important. Thus in Cooper's[46] series the mortality of 59.4 per cent when sedation was used alone was reduced to 29.3 per cent when sedation and serum were used. The type of sedation varies widely, the barbiturates being in greatest use. Sodium amytal, avertin,[56] chloral hydrate, and many other drugs have had their warm advocates. We feel that satisfactory results are obtained by the use of sodium amytal in doses of 7½ gr. repeated as often as required for narcosis.

So little is known about the amount of toxin liberated, and the host resistance in any given instance, that we feel that large amounts of antitetanic serum are necessary in the treatment of the individual case. There has been considerable discussion in the literature as to the route of administration of the serum. Recently, the intrathecal route has been added to the intravenous, intramuscular, and subcutaneous routes, and widely advocated.

Much literature has grown up about the question of intrathecally administered serum, and clinicians have differed as to its effectiveness. Gage and DeBakey,[47] Wainwright[48] and others do not advise its use. Golla[49] and Calvin and Goldberg[50] are dubious as to its value. Bates[55] uses a total of 40,000 units subcutaneously, or intravenously, and 7,500 units intrathecally as the initial dose. Vener,[53] whose mortality rate of 29 per cent in 100 cases of tetanus is perhaps the lowest reported, routinely gives 200,000 units of antitetanic serum, 40,000 units being given intracisternally. Yodh[54] uses the latter route and reports a mortality of 50.6 per cent in 443 cases. From these reports the intrathecal

administration of antitetanic serum would seem to be of definite value. More recently, the experimental work of Shumacker, Firor and Lamont[57] and of Firor[51] has tended to confirm the superior value of intrathecally administered antitetanic serum over its administration via the other routes. However, Deitrich[52] has reported the death of children following the use of intrathecally administered antitetanic serum, the clinical picture resembling bulbar poliomyelitis, or some other disease with medullary pressure or edema.

We have had little experience with the use of intrathecally administered antitetanic serum. Of the 3 patients in this series who received serum via that route, two recovered. When a patient, who has developed tetanus after a very short incubation period, and/or presents marked signs of tetanus, presents herself, it would seem to be advisable to use the serum by the intrathecal route.

The following routine may be adopted for treatment of postabortal tetanus:

1. The patient should be placed in a quiet room, shielded from noises and external stimuli. She should be given sodium amytal, gr. 7½, either orally or intravenously, depending upon the severity of the symptoms. This should be repeated at sufficiently frequent intervals to maintain the patient in a narcotized state until all danger of spasms has passed. The patient should be tested for sensitization to antitetanic serum.

2. Antitetanic serum should be administered: 50,000 units intramuscularly, 50,000 intravenously. If the incubation period has been short, or if the symptoms are severe, intrathecal administration of 50,000 units of antitetanus serum may be added to this routine. 30,000 units antitetanus serum should be given intramuscularly and intravenously on each of the next three days. Additional dosages of serum, or larger quantities may be given depending upon the clinical picture.

3. Nutrition should be maintained by tube feeding and/or by intravenous drip.

4. The bladder and bowel function of the patient should be watched. When necessary the nasopharynx should be frequently aspirated, and the patient, if narcotized for a long period, should have frequent changes of position.

The treatment of the site of injury was shown to be of importance long ago. Thus Cummins[45] was able to report a series in which a mortality of 64.4 per cent was reduced to 51.5 per cent by the use of excision of the wound and complete débridement.

With this fact in mind there has been much discussion in the literature as to the usefulness of hysterectomy as an adjunct to the aforementioned routine of therapy in postabortal tetanus. Its advocates unfortunately have been unable to demonstrate any improvement in the mortality rate of their series. Hysterectomy is certainly of questionable value. One cannot insist that it has increased the mortality or decreased the chance of survival in the particular patient. One cannot argue that, because a patient who has sustained a hysterectomy has

survived, the procedure was of value. Dilatation and curettage, or manual evacuation of the uterine contents has also been advocated by some authors, based on the principle that any tissue remaining in the uterus may contain the tetanus bacilli and spores, and so act to prolong the infection and increase its severity. However, postabortal dilatation and curettage are generally and correctly condemned.

With the same idea some authors advocate dilatation of the cervix followed by the insertion into the uterus of a large amount of antitetanic serum through a catheter. Others have advised the irrigation of the uterus with oxygen and Dakin's solution. These procedures were not used in any of the cases of our series. It is interesting to note that the patient in Case 6 in our series had a curettage which was done because of severe hemorrhage, and recovered. The prolonged incubation period in this patient (fourteen days), together with the use of intravenously and intrathecally administered serum, may account for the recovery of this patient.

The incidence of postabortal tetanus is a matter of some conjecture. In the fifteen-year period studied, Touro Infirmary had 6 cases so diagnosed out of a markedly smaller total admissions than Charity Hospital which, in the same period, had only 8 recorded cases of postabortal tetanus. The prognosis is poor. Vinay[40] reported a mortality of 89 per cent which collaborates the findings of Schneider who reported a mortality of 91 per cent and of Rubeska of 100 per cent. In Sepet's series the mortality was 86 per cent, while Auvray reporting on 41 cases (collected since Sepet's series) reported a mortality of 85.36 per cent.

In Mondor's[39] more recent series (1934) of 51 cases, the mortality was 76 per cent. It is interesting to note the very minor improvement in mortality in the reports which fall in the period during which antitetanus serum has been known and used and the reports which antedated the widespread use of antitetanus serum. In the collected literature, the mortality is approximately 85 per cent, while of the 14 cases herein reported there was a mortality of 57 per cent.

It is interesting to compare the mortality at the two institutions we have studied. At Charity Hospital two patients out of 8 recovered, a mortality of 75 per cent, while at Touro Infirmary 4 patients out of 6 recovered, a mortality of 33 per cent. While the mortality rate of Charity Hospital series is quite high it is not surprising considering the fact that patients usually present themselves for treatment later, due to the fact that many come from distant points, and due to the secrecy which surrounds the criminal procedure which they have sustained. It is this same secrecy which accounts for many more deaths from postabortal tetanus which occur in patients who probably never reach the hospital.

Although the proper emphasis has been placed upon the prevention of traumatic or surgical tetanus, there is an appalling lack of attention to the prevention of postabortal tetanus. We feel that it would be wise to administer a prophylactic dose of antitetanic serum to every woman who has submitted to a criminal abortion.

SUMMARY

1. Fourteen cases of postabortal tetanus are reported, with a mortality of 57 per cent.

2. The literature of postabortal tetanus has been surveyed and note is made of the paucity of American and English reports, and of the high mortality (90 per cent) which still persists.

3. We feel that this series should help to focus attention on the syndrome and stimulate further reports, and provoke a more careful watch for symptoms of tetanus in cases of criminal abortion.

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ENDOMETRITIS AND TUBAL ECTOPIC PREGNANCY*

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THAT endometritis frequently produces sterility is an acknowledged fact. That tubal pregnancy occurs frequently within a Fallopian tube that is the seat of a chronic salpingitis is also conceded.

For pregnancy to occur in a tube that is chronically inflamed and not to occur in an endometrium that is the site of a similar pathologic process seems contradictory until all the facts are taken into consideration. In the case of the tube, only the fertilized ovum needs to be considered. Normally the ovum progresses down the course of the tube and into the uterus by passive motion, that is, by the action of the cilia of the tubal epithelium. However, should these cilia be destroyed or should sacs produced by adhesions within the tube be formed due to the inflammatory process, the progress of the fertilized ovum may be arrested and implantation may occur within the tube.

In contrast to the passive motion of the fertilized ovum, the spermatozoa are actively motile and this autonomous locomotion under normal conditions is controlled by two environmental factors. The first of these factors is called "rheotaxis" and is closely related to physiologic reflexes. Because of this so-called reflex the sperm cells move against the current of the cervical and vaginal secretions. The second factor is the biochemical composition of the medium, particularly its pH. The spermatic fluid itself is definitely alkaline, whereas the normal vaginal secretion is markedly acid. This acidity is hostile to the spermatozoa and paralyses their motility. The vaginal acidity is high enough to exceed the alkalinity of the spermatic fluid and consequently, the mixture of spermatic and vaginal secretion is still of definite acidity. Seguy and Vimeux[1] determined the reaction of this mixture one-half hour after coitus as 6,1 to 6,2 pH. The normal cervical secretion is characterized by definite alkalinity, which by a process resembling chemotaxis, attracts the spermatozoa.

Seguy and Vimeux[1] describe a specific, thin cervical secretion produced by the cervical mucosa, especially at the time of ovulation, as being particularly favorable for the spermatozoa. The presence of this specific thin secretion at the time of ovulation offers very favorable conditions for the spermatozoa to penetrate the barrier of the cervix, thus facilitating fertilization at the time of ovulation. This observation by the two French investigators fits in very well with Knaus's theory of the coincidence of ovulation time and optimum fertilization time. However, the antagonistic influence of the acid vaginal secretion upon sperm migration should not be over-estimated. Spermatozoa if deposited at

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the vulva can reach the cervix by active migration through the entire length of the acid vagina. One of us (W. S.) had the opportunity to observe eight cases of normal pregnancies in women each with a perfectly intact hymen. In some of these cases the opening of the hymen measured only 3 to 4 mm. History confirmed by the anatomic findings gave evidence that in all of these cases the ejaculated semen had been deposited at the vulva outside of the diaphragm of the hymen. In all of these cases the spermatozoa had to pass the entire length of the acid vagina (but, possibly in some, a strong alkaline cervical secretion neutralized or even alkalinized the acid vagina), and had to migrate upward against a strong current. In both conditions the main and only important factor for transportation was the active motility of the spermatozoa. Such mechanisms as, for instance, the piston action of the penis, as described by J. Müller, the suction of the uterus during orgasm, as described by Wemich and Fehling, or the imbibition of the mucus plug with spermatozoa during orgasm and retraction after orgasm as described by Kristeller and Havelock Ellis, evidently played no role.

Seguy and Vimeux[1] point out that purulent cervical secretion is most unfavorable for the spermatozoa: "In certain women the cervical canal physiologically is never permeable for the spermatozoa, either because there is no thin mucinous secretion present, or because the secretion permanently is purulent. These facts may offer an understanding for certain unexplained cases of sterility." Similarly Kurzrock and Miller[3] emphasize the importance of the difference of electric potential between the vaginal and the cervical fluid causing a cataphoretic effect and say: "when the cervical mucus plug becomes infected it no longer shows the penetration phenomenon with semen," . . . and "if the cervical mucus is infected, very viscous, thick and opaque, the sperm in proximity to it will not accumulate at its boundary and will make no attempt to penetrate the mass."

Kurzrock and Miller[3] discovered another important factor for the passage of spermatozoa through the cervical canal, namely, the ability of the spermatic fluid to dissolve the mucus plug which physiologically protects the entrance of the external os. In cases of purulent cervicitis the mucus plug becomes resistant to the lysins of the spermatic fluid. "When frank pus was present, there was almost no digestion in 48 hours," and this explains the fact, that "a woman with an acute gonorrhea with its extensive purulent cervical discharge or with extensive leucorrhea due to tears or disease in the cervix almost never becomes pregnant as long as the discharge persists. Where the cervical mucus is only partially contaminated, considerable time may elapse before digestion is sufficient to allow spermatozoa to pass through the cervix. So that here, as above, by the time the spermatozoa have reached the tube their fertilizing power may be lost although their motility may remain. The patient remains sterile."

Many authors agree that purulent cervicitis and endometritis hamper and hinder the passage of spermatozoa through the cervical canal. In an exact analysis of this important cause of sterility, we must consider six points: (1) the current of the cervical and vaginal secretions, (2)

consistency of the cervical and vaginal secretions, (3) reaction of the cervical and vaginal secretions, (4) temperature of the cervical and vaginal secretions, (5) presence of leucocytes, (6) presence of spermatoxic substances.

1. The current of the cervical and vaginal secretions cannot be considered a definite hindrance since it is well known that a severe leucorrhea in many cases is not in itself a cause of sterility.

2. The consistency of the cervical mucus may serve as a hindrance in the case of a thick, very viscous plug of concentrated mucus as described by Kurzrock and Miller. But this does not hold when a thin, watery, purulent secretion is produced, as in some cases of acute cervicitis and endometritis.

3. The reaction of a purulent secretion is definitely alkaline. This holds true in general and has been proved in numerous cases of endometritis by Seguy and Vimeux. Consequently, purulent secretion should, at least by its reaction, facilitate the ascent and passage of spermatozoa.

4. The temperature of acute inflammatory tissue may rise even above the general temperature. Spermatozoa are delicate and sensitive to increased temperature as demonstrated by Stigler and recently by Weisman. But this holds only for increases of temperature of at least 10° or more, which far surpass those encountered in local inflammation which never amounts to more than 2 to 3°.

5. The presence of leucocytes in the vaginal and cervical secretions with specific reference to their influence upon sperm cells could not be found in the literature. However, communication with Dr. Abner Weisman of New York, who has carried out a great deal of experimental work on sperm cells, in the course of the last few years, and who has published a summary of this work in a monograph called *Spermatozoa and Sterility* (P. B. Hoeber, Inc., New York, 1941), reveals that he has tested the influence of pus cells on spermatozoa. He presented the results in an exhibit in the New York Academy of Medicine, Oct. 14 to 27, 1940, and in a short paper called "The Effect of Pus on the Survival of Spermatozoa," which is to be published soon. The sum and substance of his findings are that infection if it does inhibit sperm travel does so only by mechanical blockade due to the formation of pus clumps. Phagocytosis of spermatozoa by leucocytes does not occur, nor is their motility affected. "In vitro spermatozoa can live if mixed with pus 18 to 32 hours."

6. The presence of spermatoxic substances in the cervical and vaginal secretion and the effect which they have upon the sperm cells have been studied extensively. Metschnikoff deserves credit for having discovered the immobilizing spermatoxins produced by active immunization. Günther[5] in 1907 continued the investigations which Koelliker[6] started in 1856. He investigated the influence of more than 50 organic and inorganic compounds in various dilutions on the motility of fresh spermatozoa and demonstrated the particular high toxicity of chinin. The damaging influence of pure water on spermatozoa has recently been discovered by Weisman.[7]

I. Schiller and A. Giltscher[8] proved that in a nitrogen-free medium *B. subtilis* and some cocci produce lysin of spermatozoa, but not in normal saline solution: this observation does not meet with practical clinical conditions.

In cervical purulent secretion only toxins produced by bacteria have to be considered. Rosenthal[9] made the interesting observation that not only acids, alkalies, salts of heavy metals, carbon dioxide, dyes and so on agglutinate spermatozoa, but some strains of *B. coli* similarly cause agglutination of spermatozoa, whereas *B. typhosus, B. paratyphosus, B. proteus, B. pyocyaneus, B. subtilis,* and *B. tuberculosis* have no such properties. Le Lorier and Fisch[10] found that toxins of twenty-day-old cultures of *B. coli* had the ability to agglutinate and to immobilize spermatozoa.

Since endometritis under special conditions apparently does not prevent the ascent of the spermatozoa, the latter may reach the tube and fertilize an ovum if present in the lumen. Precocious embedding of the fertilized ovum may then occur leading to a tubal pregnancy. Such cases of combined endometritis and tubal pregnancy are rare but deserve mention for they clinically support the experimental observation that migration of spermatozoa is not prevented by a medium of purulent inflammation.

CASE REPORTS

Recently we had the opportunity to study two cases in which a tubal ectopic pregnancy was found combined with a severe endometritis. The first case, endometritis postabortum and tubal ectopic pregnancy, was found at an autopsy performed in the morgue of the Cook County Hospital; the second, we owe to the courtesy of Dr. Werthammer, Huntington, W. Va.

CASE 1.—Colored female, 28 years of age, was admitted to the Cook County Hospital with the complaints of vaginal bleeding of six weeks' duration, cramping lower abdominal pain, fever, and abdominal distention for one week and fainting once during the week before admission. For one week prior to her entrance to the hospital the patient was treated at home by a physician with the daily administration of 10 c.c. of boiled milk intramuscularly and 10 c.c. of calcium gluconate intravenously. When she did not improve, she entered the Cook County Hospital.

The patient's past history revealed a miscarriage four months before her present illness, but she denied selfinstrumentation. Otherwise her past history, as given, was negative.

She was admitted to a medical ward and six days later was transferred to a septic obstetric ward. Physical examination at that time revealed a temperature of 100.6° F.; pulse, 120; respirations, 24; blood pressure, 109/56. The conjunctivae were pale. Colostrum could be expressed from the left breast. The lungs, heart, and abdomen were essentially normal.

On pelvic examination the introitus was found to be multiparous, Bartholin's and Skene's glands and the urethra were negative, although a vaginal discharge was present. The external os barely admitted a small forceps. Pieces of tissue 1 to 2 cm. long and a few millimeters thick were protruding through the external os. The impression was that these were decidual tissue rather than placenta. The pathologist reported that they were portions of endometrium displaying a marked decidual reaction and a marked infiltration with polymorphonuclear leucocytes.

The uterus was enlarged to about the size of a two months' pregnancy. The right adenexa revealed no masses or tenderness on bimanual examination. On the left side there was an indefinite fullness which was assumed to be a mass measuring approximately 5 by 6 cm. This mass seemed to extend into the cul-de-sac and produced a bulge that was very tender on palpation.

On the day of her transfer, six days after admission, a posterior colpotomy was done and old blood, both fluid and in clots, was recovered. Because of these findings a diagnosis of an ectopic pregnancy was made and a left salpingectomy was performed on the same day.

At operation a tubal pregnancy that had ruptured through the isthmic portion of the left Fallopian tube accompanied by a massive hemoperitoneum was noted. The right adnexa and the left ovary were reported to be in good condition. The pathologist reported an acutely infected ectopic pregnancy.

Fig. 1.—Endometrium, foci of necrosis with leucocytic infiltration, in the center remnants of decidua with chorionic invasion. ×120.

Postoperatively the patient developed a bronchopneumonia. Ten days postoperatively foul pus drained through the lower part of the incision. The temperature postoperatively was septic in character; the course was progressively downhill and the patient died three weeks after operation.

The laboratory workup revealed the urine to be negative for albumin and sugar. The blood findings were as follows: the hemoglobin, 34 per cent; red blood count, 1,980,000; white blood count, 12,100; two weeks later the hemoglobin, 54 per cent; red blood count, 3,160,000; white blood count, 9,700.

Microscopic Description.—The myometrium presents a moderate edema of the intermuscular connective tissue septa as is usually found in and after pregnancy. The number of the vessels are increased, the smaller vessels are markedly tortuous. The endometrium shows in the deeper layers cystically dilated glands with flattened epithelium and cloudy debris in the lumina. The cytogenic tissue is densely infiltrated with leucocytes and this inflammatory infiltration increases toward the upper part of the mucosa, which is replaced by a thick coat of fibrin, with leucocytes in the interstices of the network. There are numerous

irregularly shaped, partially confluent foci of purulent necrosis. In the middle layer of the endometrium, remnants of necrobiotic decidua can be found. In some foci, shrunken chorionic giant cells can be seen. Some of the small arterioles and some of the glands are surrounded by thick coats of fibrin which similarly contain single shrunken chorionic cells, which are characteristic findings in endometritis postabortum (Fig. 1).

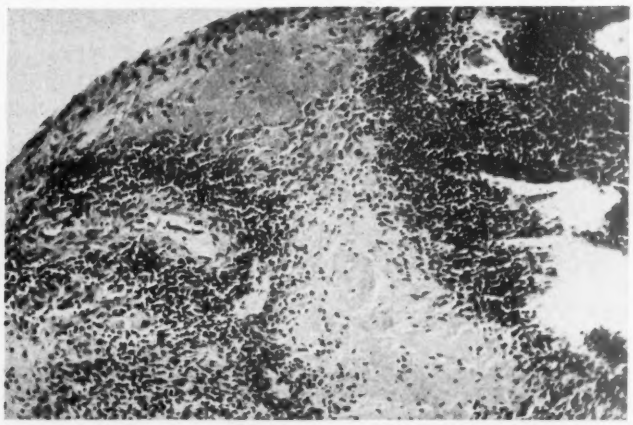

Fig. 2.—Endometrium, dense leucocytic infiltration and necrosis. ×120.

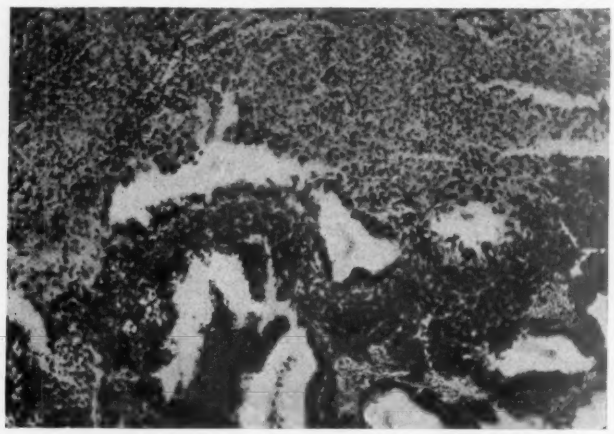

Fig. 3.—Endometrium, in the lower part involuted Opitz glands, in the upper part inactive cytogenic tissue with leucocytic infiltration. ×120.

CASE 2.—Slides of this case (M. D.) were referred to the senior author for consultation. The patient was a white female, aged 37 years, who was admitted to the hospital on June 3, 1940, with the complaints of pain in the lower abdomen of three years' duration accompanied by chills and fever. These pains were sometimes very severe. More recently she was frequently nauseated and vomited and complained of anorexia. In addition there were complaints of weight loss and weakness. Her menses were regular and for the last several months had lasted for eight to ten days instead of three to four days as they had

previously. There was no vaginal discharge. The patient's past history was negative; she had one child 14 years old, who was in good health.

On physical examination an adenoma of the thyroid, the size of an egg, was palpable on the right side. The abdomen was everywhere tender and rigid. The liver, spleen, and kidneys were not palpable, but there was tenderness over both lumbar regions. A vaginal examination was not done.

The blood count showed a hemoglobin of 69 per cent; red blood cells, 3,650,000; white blood cells, 14,000; the differential count revealed: polymorphonuclear leucocytes, 80 per cent; lymphocytes, 17 per cent; and monocytes, 3 per cent. The urine contained 2-plus albumin, and there were many red blood cells and a few white blood cells and epithelial cells.

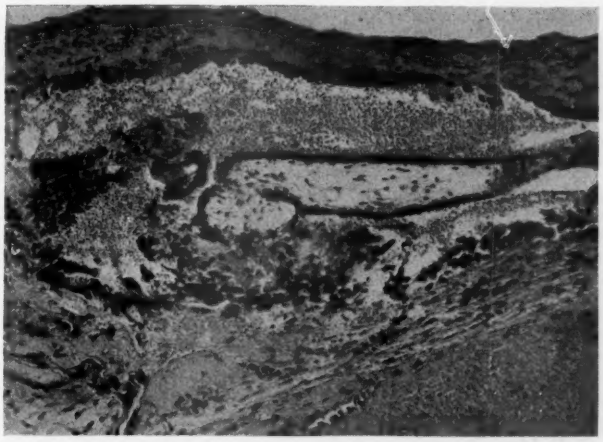

Fig. 4.—Tube, in the upper part, the thinned muscularis, in the lower part, placental villi and chorionic masses. ×120.

On the day following admission dilatation and curettage were done, and the pathologic report stated that the endometrium was of premenstrual type and no evidence of pregnancy was noted. A week later a left salpingo-oophorectomy and right salpingectomy were performed. The surgeon reported old blood and serum in the abdominal cavity with a ruptured right tubal pregnancy and a left pyosalpinx. The patient was discharged from the hospital as improved three weeks after admission.

The uterine scrapings were submitted to the senior author for microscopic examination, and he noted that there was no decidual reaction, but that there was a dense infiltration of inflammatory cells in the cytogenic tissue. The epithelium of the glands was high columnar and secreting. The lumina of the glands contained pale pink-staining secretion mixed with numerous leucocytes. The cytogenic tissue was very cellular, dense, and markedly infiltrated with leucocytes. In many areas the endometrium was undergoing necrobiotic changes and was being transformed into amorphous, pale, pink-staining masses, which were densely infiltrated with leucocytes many of which were pyknotic. A few pieces of tissue reveal such purulent, necrotic tissue exclusively with additional infiltration by red blood corpuscles (Figs. 2 and 3).

A section through the tube shows a typical tubal pregnancy with an empty collapsed amniotic cavity 11 mm. in diameter. There is a semicircular hematoma between the placenta and the tubal muscularis, which in one area is densely infiltrated by leucocytes. Over about a quarter of the periphery the tubal wall is thinned out to a few layers of muscle cells. The placental villi, mostly well preserved, present a well-developed Langhans layer and contain no vessels (Fig. 4).

DISCUSSION

Physiologically we find in tubal ectopic pregnancy a decidual reaction of the endometrium analogous to the decidual transformation of the endometrium in intrauterine pregnancy. This decidua is cast off as a triangular sac after the rupture or abortion of the ectopic pregnancy, that is, as soon as contact between placenta and maternal tissue is severed. In both of our cases no actual decidual reaction of the endometrium could be found. The few foci of decidual reaction in the first case are invaded by chorionic cells. This proves that they are remnants of the previous intrauterine pregnancy. The absence of actual decidual response to the present ectopic pregnancy can be explained as caused by the endometritis which paralyses the cytogenic cells and prevents them from responding normally to the hormones of pregnancy. Similarly in endometritis of the nonspecific generalized type, not in the focal type seen in tuberculosis, the phases of the menstrual cycle generally are suppressed and even in the premenstrual phase of highest activity, in an inflamed endometrium, tortuous and secreting glands usually are not to be seen. In the first case the chorionic cells prove that the decidua originated from the previous intrauterine pregnancy and not from the present ectopic one.

Both cases give evidence that even severe endometritis offers no unsurmountable hindrance for spermatozoa to ascend and to reach the tubes. Even the roughening of the endometrial surface and the presence of necrobiotic, cellular debris in the endometrial cavity may not prevent the migration of the spermatozoa. But, on the other hand, in cases of cervicitis when the inflamed mucosa produces thick mucin which plugs the cervical canal and at the same time is resistant to the lysins of the spermatozoa, or when clumps of pus cells obstruct the external os, complete obstruction may occur. The larger diameter of the endometrial cavity leaves enough space for the ascent of the spermatozoa even in the presence of a severe suppurative and necrotizing endometritis. Although frequently cervicitis and endometritis develop coincidently, there is no evidence of such a coincidence in the two cases. Endometritis after abortion, as in the first case, generally has no tendency to extend to the cervical mucosa. Doubtlessly conditions for intrauterine embedding of the ovum become unfavorable in case of an inflamed endometrium, although inflammation as a hindrance to implantation should not be over-estimated, since we occasionally find tubal implantation in the course of a rather severe salpingitis.

CONCLUSION

Endometritis in general prevents intrauterine implantation of the fertilized ovum, but as our two cases prove, it may not prevent sperma-

tozoa from migrating through the uterine cavity and fertilizing the ovum in the tube.

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ENDOMETRIAL POLYPOID FIBROSARCOMA

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THIS report is given for two reasons. First, there was a distinct discrepancy in the clinical diagnosis and the microscopic report in a case of recurring endometrial polyposis. As proved eventually, at the time of removal of the uterus, the clinical diagnosis of sarcoma was correct. Second, we feel that we are dealing with a definite clinical and anatomic picture which, apparently, is not sufficiently known. From the experience in our own laboratory, corroborated by the relative paucity of reported observations similar to ours, this disease, which clinically may be designated best as recurring massive endometrial polyposis of elephantiastic character, apparently is relatively rare. It was not until the uterus was removed that the clinical diagnosis of sarcoma could be confirmed histologically. At the same time, in spite of reported recurring endometrial polyps over a period of three and one-half years, there was no clear gross evidence of any actual invasive growth of this endometrial sarcoma into the myometrium. Even in the polypous tumor material removed in fair-sized pieces two months previous to the extirpation of the uterus, a definite diagnosis of sarcoma could not be made from a large number of sections taken from different parts. Our diagnosis was confirmed by Robert Meyer who was kind enough to lend us his most valuable support.

We are in the fortunate position of being able to correlate all histologic findings secured at different times over a period of three and one-half years, with the final picture taken from the extirpated uterus.

CASE REPORT

Mrs. M. B., 52 years old, white, married, a patient of Dr. James King, entered the Buffalo General Hospital on Oct. 20, 1937, with the following history: her chief complaint was brownish, stringy discharge from the vagina of six weeks' duration. Her last menstrual period was in December, 1936. She had apparently been well until she noticed this scant, foul-smelling, brownish, stringy discharge. There were no complaints of pain but itching and irritation of the skin adjacent to the

vagina were present. Thirteen days before admission to the hospital the discharge increased in amount, requiring one perineal pad during the day and one at night. Three days before admission she noticed a mass protruding from the vagina.

The past history revealed a loss of 50 pounds in weight during the past ten years; otherwise the remainder of the history was not pertinent except for diabetes, treated by diet and insulin therapy.

Fig. 1.

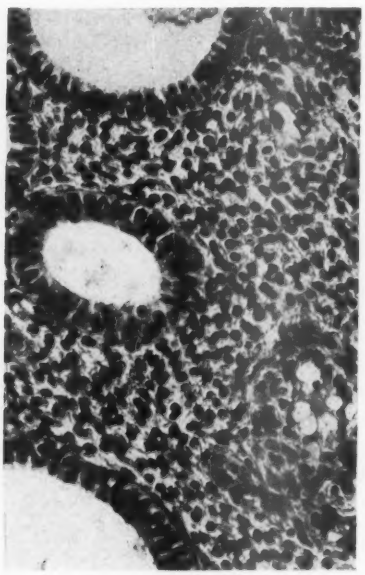

Fig. 2.

Fig. 1.—Very low power view of the entire polyp.
Fig. 2.—Medium power view of a typical part within the polyp.

The physical examination was not remarkable except for a diffusely enlarged thyroid gland and the gynecologic examination which revealed a necrotic, infected, prolapsed uterine polyp.

On Oct. 21, 1937, under cyclopropane anesthesia, the polyp (Fig. 1) was removed and the cavity of the uterus was packed with gauze. An uneventful recovery followed.

Microscopic diagnosis was that of a typical glandular, cystic endometrial polyp (Fig. 2) which was not malignant. A smaller fragment from the cervix showed slight edema and fibromatous hyperplasia of the stromal cells.

The patient's next admission was Sept. 26, 1938; approximately one year later. She complained now of a polyp protruding from the introitus, which had been bleeding for two or three days before admission.

Under cyclopropane anesthesia, a broad fingerlike polyp was removed from the lower uterine segment. The cervix was dilated and a polyp forceps, introduced into the cavity, brought away several polyplike structures, the largest of which was the size of a walnut. The patient was discharged in good condition on the third day.

Pathologic Diagnosis.—Gross inspection revealed four edematous polyps measuring from 3.5 by 2 cm. to 5.5 by 3 cm. in thickness. Microscopic examination showed glandular cystic cervical polyps with marked edema of the stroma (Fig. 3) and injection of the capillaries, slight hemosiderosis, and slight hyalinization. The glands contained mucoid secretion. In one of the polyps there were scattered atypical endothelial cells in the stroma. No reference was made to malignancy.

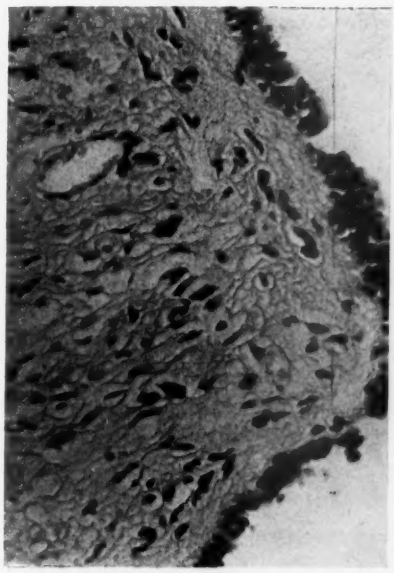

Fig. 3.

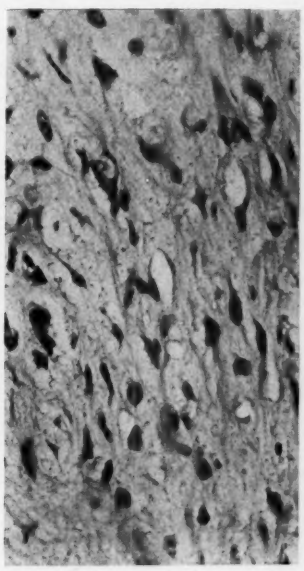

Fig. 4.

Fig. 3.—Medium power view of the somewhat fibromatous and edematous portion of the polyp near the surface epithelium.

Fig. 4.—Medium power view, showing a fibromatous portion of the polyp with distinct edema.

Patient's third admission was Aug. 5, 1940, three years after the removal of the first polyp. At this time her history revealed the interesting fact that on seven different occasions polyps described as "the size of a finger" had been removed by her physician in his office. One week before this admission the patient complained of cramplike lower abdominal pains and again the presence of a mass protruding from the vulva. Bleeding of moderate degree was also present.

On the day following, under cyclopropane anesthesia, an olive-sized, gangrenous appearing polyp was removed from a wide base at a point midway up on the right side of the uterine cavity. A number of smaller polyps were easily removed with the ring forceps. Radiation with radium (500 mg. hours) was given.

Pathologic Diagnosis.—Specimens include several polyps from uterus and several large fragments of tissue. On cut section tissue was soft and grayish yellow in color with extensive hemorrhages present.

Microscopic diagnosis revealed markedly edematous polyps, containing a moderate number of glands. The surface epithelium was still preserved, with occasional papillary protrusions. A number of recent hemorrhages were present. Some of the sections showed a marked preponderance of stroma with almost fibromalike structures (Fig. 4).

Her last admission was Dec. 27, 1940. At this time she complained of having had occasional "spotting" since her last admission. A yel-

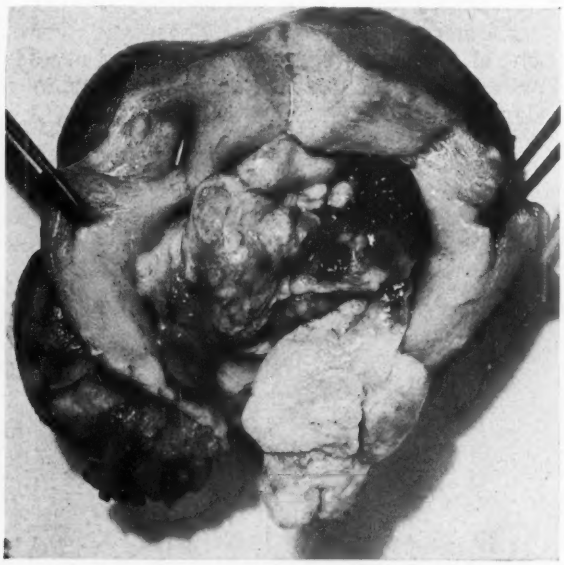

Fig. 5.—Opened uterus with the cavum almost completely filled by huge, slightly lobulated polyps.

Fig. 6.—Sagittal plane through the uterus, showing intramural fibroids and huge polyps with hemorrhages, especially in the protruding one.

lowish discharge was also present. Once again she complained of protruding masses from the vagina. On this admission she showed symptoms of hyperthyroidism and for the first time her diabetes presented difficulties in management and, while waiting for its control, additional polypoid tissue was removed on three different occasions. Finally on Jan. 23, 1941, under avertin-cyclopropane anesthesia, a supravaginal hysterectomy was performed by Dr. James King. The specimen which was removed forms the basis for the present study.

Macroscopic Examination.—(Figs. 5 and 6.) Polypous and papillary, firm structures, measuring 10 by 7 by about 2 cm. Amputated corpus uteri, already dissected; weight 430 Gm. (measurements of entire specimen 10 by 12.5 by 7 cm.). Showed several pea to lemon size, subserous fibroids with hyalin and calcific degeneration in the two larger ones. Within the cavum uteri was suspended a huge, papillary, polypous mass of endometrial tissue, in some places distinctly hemorrhagic. Base of this mass was apparently firmly adherent to the uterine wall.

Fig. 7.—Very low power view through one of the huge polyps and the myometrium close by, including one intramural fibroid.

Microscopic Examination.—On a section taken through the bulk of the polyp, including its stalk and the adjoining wall of the uterus (Fig. 7), the following picture was seen: The stroma of the polypous structure was made up of proliferating mesenchymal cells, many of which had the form of long spindle-shaped fibroblasts. In many areas there was far-progressed production of collagenous fibers with hyalinization and also quite diffuse necrosis. Near the surface epithelium, as well as in the deepest areas, and most marked in the stalk, there was a frankly sarcomatous picture consisting of spindle-shaped cells as well as polymorph cells and quite a number of giant cells containing from 2 to 4 closely packed nuclei (Figs. 8, 9, 10, and 11). Here and there the delineation between myometrium and endometrium was indistinct and especially the sarcomatous portions seemed to infiltrate superficially the myometrium close by. Glands were scattered over the substance of the huge polypous structure in relatively small numbers. Some of them were evidently compressed while a few were somewhat cystically dilated. They were lined by columnar epithelium which in the dilated glands was

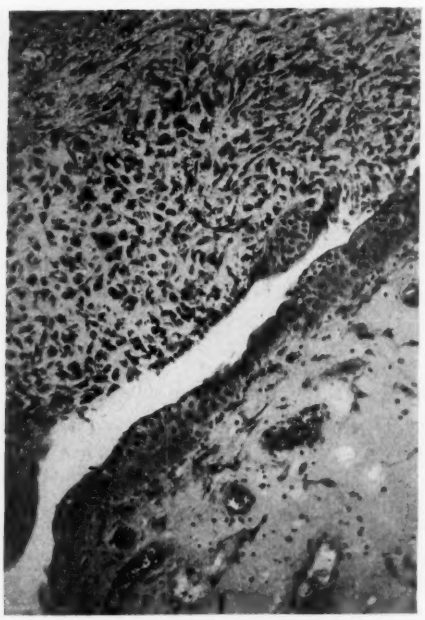

Fig. 8.

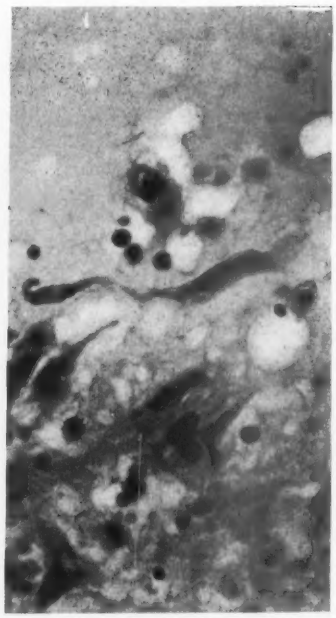

Fig. 9.

Fig. 8.—Medium power view of the sarcomatous polyp, including a deep endometrial niche lined in part by metaplastic squamous epithelium. The lower part to the left shows frankly sarcomatous, the upper to the right a simple fibromatous and markedly edematous, pattern.

Fig. 9.—High power view of a fibromatous polyp with edema.

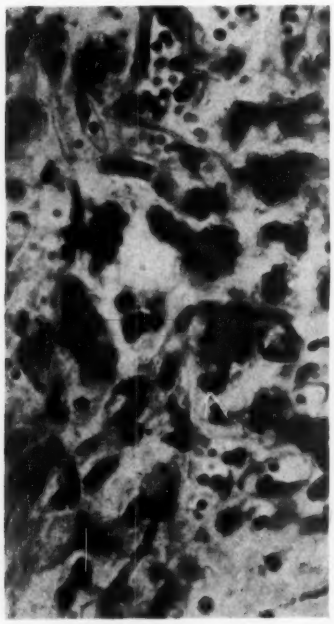

Fig. 10.

Fig. 11.

Fig. 10.—High power view of a sarcomatous section with many peculiarly shaped giant cells.

Fig. 11.—High power view of an area of edematous, fibromatous structures merging with sarcomatous giant cells.

flattened by pressure. The surface showed hyperplastic squamous epithelium, in some areas with attempts at keratinization. The fibroids in the wall were rather cellular but otherwise typical leiomyomas. The fibrosarcomatous proliferation was, for the most part, limited to the stroma of the endometrium. Again in many areas the complete hyalinization and absence of any atypical cell was bringing about a rather complex histologic picture on a cross section through the entire polyp. Finally there were many recent hemorrhages in the subepithelial surface areas and also occasional evidence of previous hemorrhages in the form of hemosiderin globules free and in huge macrophages.

Diagnosis.—Sarcomatous endometrial polyposis, in some areas of mature, plain fibromatous pattern with elephantiasis-like edema and with localized necrosis.

DISCUSSION

In searching the literature for this type of apparently relatively benign, endometrial, sarcomatous polyposis, we found only a few cases which seem to correspond to ours. Fellander[1] in his report of a case of polyps of the uterus speaks of "elephantiasis endometrii fibrosarcomatosa gigantocellularis." The patient was forty-eight years of age and complained of a bloody discharge for more than four months, following her last menstrual period. A polypoid transformation of the entire endometrium was found. One hazelnut size and one walnut size polyp, and in addition one 1 cm. long polyp about the thickness of one's index finger, were described. All of the polyps were rather soft and some showed hemorrhagic infarction in their distal end. One had a central cyst. There was no invasion into the myometrium. Microscopic examination of this tissue showed many benign looking, fibrillar structures in which there were occasional giant cells. This, it was felt by Fellander,[1] did not conform to the usual picture of sarcoma. Therefore, he called it elephantiastic fibrosarcoma. This patient was followed for seven years; she remained in good health and had no recurrence. Wollgren[2] described a similar case but without giant cells. One case which, we feel certain, is very similar to ours, is the second case in the series "polypoid adenoma of the uterus" by Strong.[3] The entire mucosa of the uterus was replaced by a polypous, villous growth. It is interesting to note that in a number of sections a mere adenomatoid picture of the uterine mucosa was seen. The stroma in these sections was rather fibrous, but in some other, separately received, sloughed off tumor particles there was a more solid mass of cells with great irregularity and many giant cells and only traces of glands. This tumor recurred in the stump in four months and grew rapidly. It was checked by radium for a time but not lessened. Figs. 4, 5, and 6, from Strong, prove better than the description, the sarcomatous nature within glandular polyposis in his case. In Novak's recent edition on *Gynecologic and Obstetric Pathology*,[4] we find the following statement on endometrial sarcoma: "The endometrial sarcoma not infrequently assumes a polypous architecture." According to Novak, the sarcomatous polyps are bulkier, denser, and more friable than the common benign variety. In this connection we wish to state that in our case close, careful gross inspection of the many polypous pieces received previous to the total extirpation of the uterus in no way revealed a sarcomatous character. Our impression was rather that of chronic edema in fibromatous polyps. Unconsciously following the terminology used in the scanty literature

on this type of tumor, our report used the same gross and histologic descriptive criteria which are apparently characteristic of these recurring polyps, namely, the elephantiasis-like picture.

Our impression that this peculiar polypous type of endometrial sarcoma is apparently uncommon or possibly not recognized even in a large amount of material is supported by the absence of this type in a series of 20 cases of sarcoma of the endometrial stroma reported by McDonald, Broders and Counseller[5] from the Mayo Clinic.

The clinical course preceding the extirpation of the uterus and the gross picture with but superficial infiltrative growth in association with the histologic picture tending in many areas toward firm fibrosis, lead us to expect a favorable prognosis for our patient as far as recurrence or metastases from this sarcoma are concerned.

Re-examination of all previous slides leads to the following conclusions: the histologic picture of an edematous fibrosarcoma was unquestionably present already at the first examination more than three years previous to extirpation of the uterus. In some areas of the polyps removed from the extirpated specimen there are almost identical pictures with those seen at the first and second examination. In fact, the few atypical cells, which at that time were thought to be endothelial cells, seem in one polyp to be really young, large, atypical fibroblasts. These same cells are massed in considerable numbers in the frankly sarcomatous areas seen in the basal parts of the polyp within the extirpated uterus. It was apparently confusing that this so-called fibromatous polyp was seen together with a typical glandular adenomatous polyp within the same curetting, and in this latter typical glandular polyp there is no evidence of fibromatous proliferation of the stroma. It is very impressive now in re-examining all the slides that the endometrial stroma had changed in all polyps into a firm, proliferating, fibroblastic blastoma with very distinct tendency to hyalinization and with that highly characteristic circulatory disturbance which is responsible for the elephantiastic appearance and which is caused by chronic edema. It is this intercellular fluid which gives the tumor cells frequently a stellated appearance, and this might explain that some pathologists use the term of fibromyxosarcoma which, however, hardly seems justified, as there is no true mucin like there is in a real myxoma.

The extensive necrosis seen in a few polyps removed two months preceding the extirpation of the uterus did not change our initial impression of an entirely benign tumor, inasmuch as in the nonnecrotic parts the histologic type was that of an entirely mature fibroblastoma with hardly any irregularity in size and chromatin content of nuclei.

Clinical course, as well as the ultimate picture of a good-sized polyp firmly fixed within the endometrium of the wall of the uterus, justify the conclusion that this endometrial polypoid sarcoma has a very marked tendency to fibrotic regression, in spite of the fact that it is a continuously, actively proliferative, true sarcoma of fibroblastic type with considerable tendency to formation of giant cells. It is expected that after this total extirpation of the uterus the course of the patient should be uneventful. We feel the name of massive, polypoid, elephantiastic fibrosarcoma of the endometrial stroma designates the most conspicuous gross and histologic characteristics of this tumor.

The authors wish to express their appreciation to Dr. James King and to Dr. Kornel Terplan under whose direction this paper was prepared.

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HYDATIDIFORM MOLE FOLLOWING TUBAL PREGNANCY

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PRIOR to June, 1938, only 35 cases of primary chorionepithelioma of the Fallopian tube had been reported.[1] Since that time, however, the reports of 7 more cases have appeared. In view of the number of cases of this malignant tumor, it is surprising to find so few recent reports of hydatidiform mole following tubal pregnancy. In theory, this lesion should be many times more common than chorionepithelioma. Meyer[2, 3] in 1918, and Mall and Meyer[4] in 1921, in reviewing the material of the Carnegie Embryological Collection, stressed the fact that early changes characteristic of hydatidiform mole are frequently overlooked, both in aborted material from the uterus and in specimens of tubal pregnancy. Hydatidiform mole may, therefore, occur more frequently than is usually supposed.

A review of the literature as far back as 1918, has been made in an attempt to arrive at an estimate of the incidence of primary tubal mole. There is considerable difference of opinion as to the criteria for diagnosis in borderline cases, both in tubal and in uterine mole. Therefore, the figures given for the incidence of these conditions vary widely with different authors.

Ewing[5] mentions 12 cases of chorionepithelioma following pregnancy in the Fallopian tube, but does not speak of tubal mole. Goodall[6] in the Davis *Obstetrics and Gynecology,* states that hydatidiform mole primary in the tube is exceedingly rare, but gives no specific details. Schumann[7] in the Curtis *Obstetrics and Gynecology,* remarks that in theory tubal mole should be fairly common. In estimating its incidence, Schumann, as well as Novak,[8] quotes the statistics previously given by Meyer[2] in 1918. The latter author[2, 3] found 7 cases in the literature and added 48 of his own. Three years later, in collaboration with Mall, Meyer[4] gave the incidence of hydatidiform degeneration in tubal pregnancies as 34 per cent, or 45 cases out of 153 studied. His diagnostic criteria, according to Novak,[8] however, were open to question, since he based his conclusions on the presence of certain stromal and vascular changes believed by him to be characteristic of early mole. These changes alone are not accepted by all pathologists as definite evidence of mole formation. His percentage may, therefore, be presumed to be somewhat high. In the opinion of Phaneuf,[9] hydatidiform degeneration occurs in about 3 per cent of all cases of tubal pregnancy, but he gives no specific data concerning actual case histories. In this same paper, Phaneuf reports 9 cases of mole seen in his personal experience, all of which were of intrauterine origin. Sherman[10] in a report of 78

cases of hydatidiform mole, found only one of these in the Fallopian tube. King[11] reported one case of tubal mole, and emphasized the value of the Aschheim-Zondek test as an aid in diagnosis. Four other scattered reports of single cases have also appeared in the foreign literature.

A recent paper by Hertig and Edmonds[12] on the "Genesis of Hydatidiform Mole" summarizes the results of a study of a large number of aborted (uterine) specimens. These authors feel that, although the typical advanced intrauterine mole of pregnancy is a relatively rare disease (1 in 2,062 deliveries), not enough emphasis has been placed on the origin and evolution of hydatidiform changes in early pathologic pregnancies. They found pathologic or so-called "blighted" ova in almost 50 per cent of spontaneous abortions in their material. They describe in detail their classification of these, and the transitional changes observed in early hydatidiform degeneration. It has been noted that pathologic embryos (and often absence of embryos) are frequently found in tubal pregnancies, and these pregnancies are of necessity relatively early. It seems probable that hydatidiform changes are present in tubal pregnancies more often than is generally believed, and the possibility should be kept in mind.

We wish to report a case which falls, we believe, in the category of true hydatidiform moles and not in the transitional group. The three accepted characteristics of this condition are present: (1) Trophoblastic proliferation, (2) liquefaction and degeneration of the villous stroma, and (3) scantiness or absence of blood vessels in the villi.

The history is as follows: A 29-year-old white married woman was admitted to the Albany Hospital, on the Service of Dr. M. J. Stapleton, on Aug. 17, 1938. Her chief complaint was of right-sided lower abdominal pain of one week's duration. She had been married for seven years and had never become pregnant. Her menstrual periods had always been regular, occurring every twenty-eight days, lasting two days, and being accompanied by moderate dysmenorrhea.

Her last regular period had occurred on May 30, 1938. She missed the June period, and on July 7 she started to have moderate vaginal bleeding. The bleeding was thought to be her normal period as she had the mild abdominal cramps which usually occurred at this time. However, she continued to bleed intermittently during the rest of July, requiring 2 pads daily. At no time was the hemorrhage severe. She continued also to have occasional cramps, but no incapacitating pain.

By August 11, the bleeding had decreased. The abdominal pain became localized to the right lower quadrant and was now almost constant. It increased in severity during the following week, and increasing constipation developed. The patient worked as a practical nurse until the day before admission. She then called a doctor, who sent her at once to the Hospital.

Examination of the patient revealed a uterus of normal size, a tender mass in the right adnexal region, and a normal left vaginal vault. Her general physical condition was good, admission temperature 99° F., pulse 90, and respirations 20. The red count was 3,400,000, and the white count 10,000. The blood Wassermann test was negative. No preoperative Aschheim-Zondek test was done. A diagnosis of ectopic pregnancy was made and a laparotomy performed.

At operation, a mass 3 cm. long, with a diameter of 2.5 cm., was present in the midportion of the right Fallopian tube. The tubal serosa over this mass was bluish in color but showed no evidence of perforation. A

small intramural myoma was present in the right cornu of the uterus. Right salpingectomy, myomectomy, and appendectomy were done. The patient made an uneventful convalescence.

On gross section, the dilated portion of the Fallopian tube contained granular friable material, portions of which were described as cystic. No fetus was seen.

On microscopic section, the tubal mucosa showed a marked inflammatory reaction, and many polymorphonuclear leucocytes were seen in the lumen of the tube. The site of the pregnancy showed markedly swollen chorionic villi in some areas, with liquefaction and degeneration of the stroma (Figs. 1 and 2). Other villi were sur-

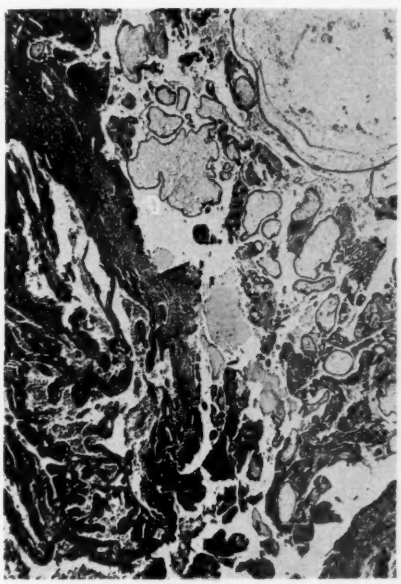

Fig. 1.

Fig. 2.

Fig. 1.—Section through tubal wall, mucosa and hydatidiform mole. The tubal mucosa is acutely inflamed. The swollen avascular villi and masses of proliferated chorionic epithelium are characteristic of hydatidiform mole. See Figs. 3 and 4. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (×11.)

Fig. 2.—Section through another portion of the hydatidiform mole. Note the masses of Langhans' cells and of syncytium. The stroma of the villi shows liquefaction and blood vessels are scanty or absent. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (×11.) Area "A" magnified ×66 is seen in Fig. 3, and Area "B" magnified ×66 is seen in Fig. 4.

rounded by piled-up masses of Langhans' cells and syncytium (Figs. 2, 3, and 4). No blood vessels were seen in these villi, although the duration of the pregnancy was ten to eleven weeks. Because of the striking hyperplasia of the chorionic epithelium, the possibility of malignancy, either actual or potential, was brought to mind.

A two-year follow-up on the patient showed that she presented no further symptoms, and a recent negative Friedman test tends to confirm the diagnosis of benign hydatidiform mole, rather than the malignant or so-called destructive mole. There is no evidence of invasion of the villous stroma by chorioepithelial elements. The Langhans' cells and syncytium, although markedly hyperplastic, are rather evenly arranged, and do not vary much in size, shape, or staining reaction. There

is no definite tissue culture-like growth of detached masses of chorionic epithelium. There is little penetration of the tubal wall in the sections studied.

In conclusion, because of the recent interest in tubal chorionepithelioma, it seems timely to report this case of hydatidiform mole primary in the Fallopian tube.

Fig. 3.

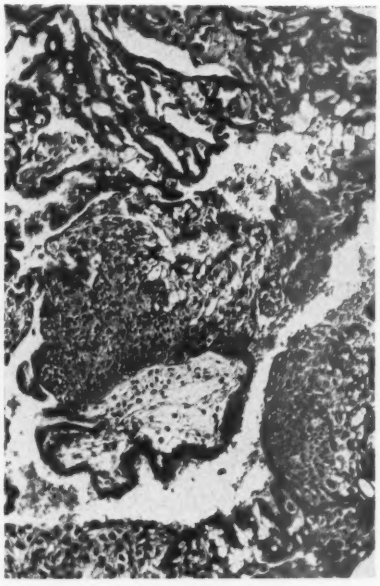

Fig. 4.

Fig. 3.—Area "A" in Fig. 2. Note the marked proliferation of the chorionic epithelium, especially the Langhans' cells. The stroma shows liquefaction degeneration and no blood vessels are seen in these villi. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (×66.)

Fig. 4.—Area "B" in Fig. 2. This section through the mole shows marked proliferation of the trophoblastic elements, especially the syncytium. *Syn.*, Syncytium; *Lan.*, Langhans' cells; *St.*, stroma. (×66.)

The unusually marked proliferation of the chorionic epithelium covering the villi in this case would make one suspicious of malignant potentialities in this tumor.

The author wishes to thank Dr. M. J. Stapleton for his permission to use the clinical history of this case, and Drs. A. W. Wright and C. F. Graham for their helpful advice.

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ARRHENOBLASTOMA OF THE OVARY

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BECAUSE of the relative infrequency of masculinizing tumors of the ovary, this case is worth reporting. Novak[1] has gathered a total of 51 cases. Since then cases have been reported in the literature by Canelo and Lisser,[2] Dockerty and MacCarty[3] and others.

Meyer,[4] who has contributed considerably to the recognition of this unusual type of tumor, points out the variability of the histologic findings of arrhenoblastoma. Novak,[5] in his description of arrhenoblastomas, describes three types of histologic variations, namely the highly differentiated form (testicular adenoma of Pick), the highly undifferentiated variety in which the histologic picture resembles that of a sarcoma, and the third form which is termed the intermediate group whose diagnostic criteria, such as tubule formation and occurrence of interstitial cells, are developed to a greater or lesser degree.

We would like to report a case showing the intermediate type of arrhenoblastoma of the ovary. The patient, E. B., 47 years of age, was admitted to the Cook County Hospital on Aug. 7, 1940. She stated that she was perfectly well until February, 1940, when she first began to experience backaches. These pains were fairly mild until March 4 of the same year when they became more severe and at the same time her abdomen became distended. On March 22, 1940, her physician tapped her abdomen and removed a considerable amount of yellow fluid. This relieved her pain considerably. The patient found it necessary to be tapped on three other occasions before entering the hospital for further treatment. In the past six weeks she has noted a slight growth of hair in the chin area associated with fall of hair from the head.

The patient's menses began at 15 years and 4 months of age; the frequency was regular, every twenty-eight days, up to August, 1939. The flow was profuse for the first two days and tapered off gradually, the entire period lasting eight days. One week after cessation of the normal flow in August, 1939, a slightly bloody flow was noted and this lasted for two days and ceased. Thereafter the patient menstruated regularly until January, 1940, when she developed an amenorrhea until Aug. 7, 1940, the day she entered the hospital. At that time she had a scanty flow.

The patient was pregnant one time and delivered spontaneously, the labor period lasting only three and a half hours.

Physical examination revealed a well-developed, well-nourished white woman lying comfortably in bed and not acutely ill. The pulse was 96, the temperature 99.4° F., respirations 24, and the blood pressure 108/80. The scalp was normal. Pupils reacted to light and accommodation; there was a slight suggestive lid lag and exophthalmus. The chin showed a slight hirsutism. The thyroid was not palpable. The

chest showed atrophy of the breasts with distribution of hairs particularly about the areola. The lung findings were normal. On percussion the heart was found to be within normal limits; on auscultation a soft systolic murmur was heard over the apex and aortic areas.

The abdomen was distended and a distinct fluid wave was elicited. The liver, kidneys, and spleen were not palpated. In the lower abdomen a hard, ballotable mass about the size of a five and one-half months' pregnancy was palpated. The gluteal regions showed slight atrophy of the fat tissue, and there was slight pitting edema of the legs.

Pelvic examination revealed a slight hypertrophy of the clitoris. The introitus admitted two fingers with ease. The Bartholin and Skene's glands and urethra were negative. Vaginal examination, following abdominal paracentesis in which 8,500 c.c. of a straw-colored fluid was removed, revealed a softened, lacerated cervix pointing posteriorly and to the right. The corpus uteri was fairly firm and not enlarged. A smooth, moderately firm, nontender mass the size of a five months' pregnancy was palpated. It was difficult to determine whether this mass was attached to the uterus or lay adjacent to it. The mass was somewhat movable and the adnexal structures were obliterated by the mass.

Laboratory Findings.—Red blood cell count was 3,800,000 per cubic millimeter; hemoglobin 72 per cent; white blood cell count was 11,500; differential count revealed 87 per cent polymorphonuclear leucocytes, 10 per cent lymphocytes, and 3 per cent monocytes. The Kahn and Wassermann tests were negative. The urine was negative for sugar and albumin.

X-ray films of the chest showed a small amount of infiltration in the lungs, probably due to passive congestion. X-ray picture of the abdomen showed no radio-opaque shadows.

In view of the clinical and physical findings, a masculinizing tumor of the ovary was considered by Dr. H. Isaacs of the Medical Department.

The patient was transferred to the Gynecological Service of one of us (A. E. K.), and she was operated upon on Aug. 20, 1940. A right ovarian tumor the size of a five months' pregnancy was exposed following the removal of 10,000 c.c. of yellow serous ascitic fluid. The uterus was enlarged to the size of a two months' pregnancy. A bilateral salpingo-oophorectomy and a supracervical hysterectomy were performed; 1000 c.c. of saline were instilled into the abdominal cavity before closure.

The patient made an uneventful recovery and six weeks after her operation the hairs of the chest and chin disappeared and the clitoris returned to normal. No ascites was noted since the operation.

Pathologic Report.—The specimen consisted of a uterus amputated above the cervix, both tubes, and both ovaries. The uterus, previously opened, measured 7 by 6 by 4 cm. The myometrium measured up to 2.5 cm. in thickness; the consistency was firm and light tan gray in color traversed by grayish white lines. The endometrium measured up to 1 mm.; it was firm and reddish gray in color. The fimbriated ends of both Fallopian tubes were patent. The walls were slightly thickened and the mucosa was light gray in color.

The left ovary measured 3.5 by 2.1 cm. On section it contained a previously opened cyst filled with a brownish serous fluid and numerous corpora albicantia. The right ovary was transformed into a tumor mass and measured 15 by 17 by 11.5 cm. Except for a 7 cm. circular area which was roughened, the surface of the ovary was smooth and

light purplish-red in color. The sectioned ovary was composed of a mushlike purplish gray to greenish gray necrotic tissue which in places, particularly in the center of the mass, was partially liquefied (Fig. 1). In other places in the periphery of the tumor where the tumor tissue was not degenerated, ill-defined nodular areas light yellowish gray mottled by areas of purplish gray color were noted.

Microscopic examinations were made from different areas of the ovarian tumor as well as from the opposite ovary and from the uterus. The sections were stained with hemalum and eosin, azocarmine, Van Gieson, sudan III, Gamori, Mallory phosphotungstic hematoxylin, and iron hematoxylin. In addition, unstained frozen sections of the tumor were studied by means of the fluorescence microscope.[6]

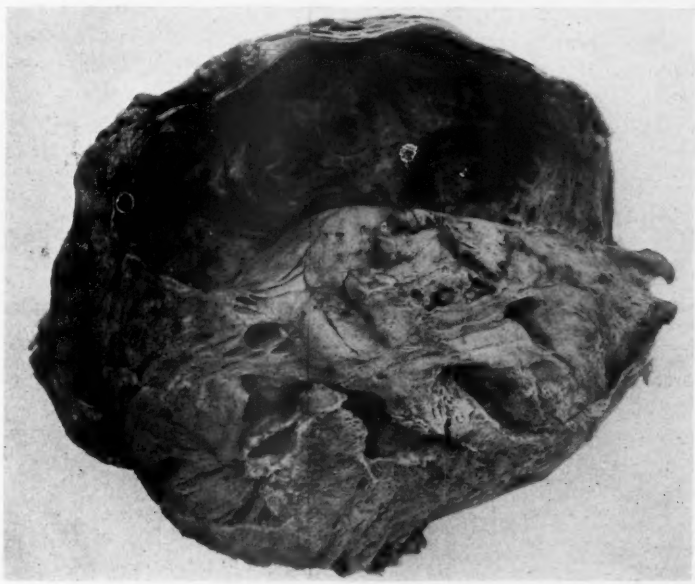

Fig. 1.—Cut section of arrhenoblastoma of ovary showing cystic areas in the tumor due to liquefaction of necrotic tissue.

Throughout the ovarian tumor, in addition to large focal areas of necrosis, there were seen several different types of glandular arrangement. One type was composed of a papillary process which in places appeared to show fusion of the processes forming small racemose-like structures (Fig. 2). These glands were lined by several layers of cuboidal epithelial cells. The cytoplasmic membranes of those cells were rather indistinct. The nuclei were round to oval shaped and coarsely granular. Other glands were distended, round to oval in shape (Fig. 3) and were lined by single layers of high cuboidal cells with fairly large round nuclei which were distinctly vesicular but in places resembled the cell lining described in the glands above. The cytoplasm of some of these cells contained sudanophilic droplets, and nearly all of the cells contained phosphin 3 R droplets as demonstrated by the fluorescence microscope. The lumina of these dilated glands were filled with desquamated cells whose nuclei had undergone pyknosis and karyorrhexis and contained also amorphous debris and coagulated pink-stain-

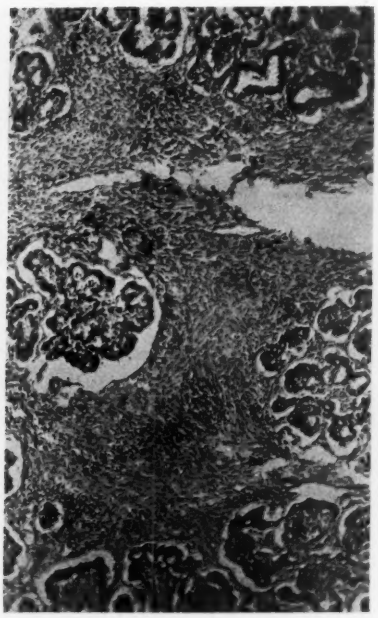

Fig. 2.

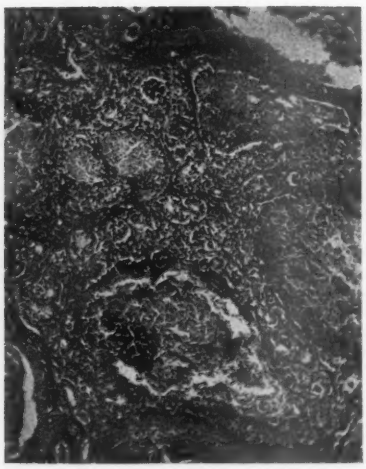

Fig. 3.

Fig. 2.—Hemalum eosin stain photomicrograph showing papillary racemose-like gland structure. (Mag. ×76.)

Fig. 3.—Hemalum eosin stain showing large dilated glands lined by high cuboidal epithelial cells containing amorphous debris in the lumen and the small tubular glands in the center lined by low cuboidal epithelium. (Mag. ×76.)

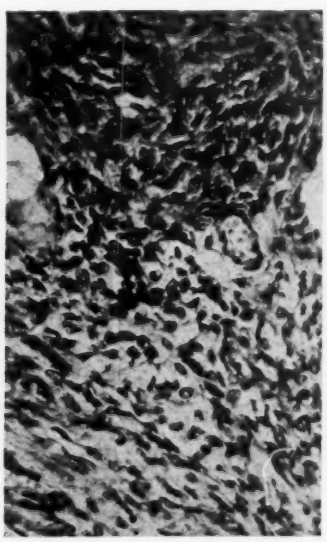

Fig. 4.

Fig. 5.

Fig. 4.—Hemalum eosin stain showing clumps of foam-like cells in the interstitial tissue resembling the interstitial cells of Leydig. (Mag. ×320.)

Fig. 5.—Hemalum eosin stain showing atrophy of the endometrium and single cystic endometrial gland. (Mag. ×76.)

ing material. The third type of gland was small and at times distinctly tubular in character. They were lined by low cuboidal epithelium (Fig. 3) whose cytoplasm was more pale than the larger glands described above. The nuclei, however, were similar to the nuclei of the first group of glands described, except possibly for a more marked elongation. The interstitial tissue for the most part was composed of a loose edematous connective tissue which was quite cellular and contained few reticulum fibrils scattered throughout the interstitial tissue. Particularly in the region about the smaller glands were single or groups of foamlike cells (Fig. 4) filled with sudanophilic material which was rich with a bright green-fading vitamin A fluorescence as demonstrated by the fluorescence microscope. After the fading of the vitamin A fluorescence, a stable brownish ultraviolet fluorescence remained. In addition, anisotropic lipoid droplets were present in these cells. These cells resembled the interstitial Leydig cells of the testicle. The capsule of the tumor was composed of edematous connective tissue and had completely lost the characteristic appearance of the cortex of the ovary.

Section of the other ovary revealed numerous corpora albicantia and no apparent primordial ova in the cortex. In one area was a small cyst lined by large cells, containing brown pigment granules.

Section of the uterus revealed an atrophy of the endometrium (Fig. 5) with single large moderately dilated glands lined by a tall columnar epithelium containing more or less centrally placed round to oval-shaped vesicular nuclei. The endometrial stroma appeared to be moderately fibrotic. The myometrium was unchanged.

In view of the above pathologic finding, a diagnosis of an intermediate type of arrhenoblastoma was made.

SUMMARY

A case of an arrhenoblastoma of the ovary is reported. It is characterized clinically by symptoms of defeminization as characterized by atrophy of the breast and fat of the gluteal region and symptoms of masculinization as characterized by hirsutism and hypertrophied clitoris. From a pathologic point of view, the diagnosis of arrhenoblastoma of the ovary is greatly enhanced by the use of the fluorescence microscope which enables one to demonstrate more definitely those cells which resemble the interstitial cells of Leydig as seen in a testicle.

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FIBROSARCOMA OF THE BUTTOCK ASSOCIATED WITH PREGNANCY

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THESE two cases are reported because of the rather unusual association of fibrosarcoma of the buttock and pregnancy. The cases varied widely as to treatment and outcome.

The first case is unusual in that the tumor arose in the gluteal region, and by direct extension encroached upon the birth canal. Dystocia due to tumors, of course, is not rare, but most often the tumor arises from a pelvic structure, myomata,[1] ovarian tumor,[2] or the bony pelvis itself.[3] The second case presented no dystocia.

CASE 1.—B. H. (No. 2335), a 42-year-old white gravida, was first seen in the clinic at the Hospital, Dec. 18, 1940. She was referred by her family physician because of a painful swelling in the left buttock which appeared as a small lump three and one-half years previously. Following an unsuccessful attempt at excision elsewhere six months previously, the tumefaction had evinced accelerated growth. Histologic examination by the consulting pathologist showed a sarcoma.

Examination revealed a moderately anemic and emaciated woman. A hard, irregular, tender mass approximately 15 cm. in diameter which was fixed to the skin but not to the bone presented in the left buttock. The mass invaded deeply into the gluteal muscles and ischiorectal fossa medially to the vaginal wall with resultant narrowing of the outlet and vagina. The patient was found to be seven months pregnant; the expected date of confinement was estimated as being Feb. 27, 1941. The patient had had four previous pregnancies, all of which were normal and terminated in uneventful deliveries. The fetal position was occiput anterior; the head was floating and fetal heart tones were normal. Pelvic measurement revealed a diagonal conjugate of 12.5 cm. The tuberosities could not be accurately measured because of tumor growth over the left tuberosity; however, the distance between the right tuberosity and the resistant borders of the neoplasm on the left was approximately 5 cm.

The patient was admitted to the hospital Jan. 11, 1941, with no change in the above findings except for some increase in size of the tumor which was not rebiopsied here because of a desire to avoid a fungating mass through the incision. The fetus was found to be viable. Roentgenograms revealed no evidence of local or remote osseous involvement. The Kahn was negative.

It was the consensus of opinion that the malignancy was advanced beyond any hope of effective specific therapy, the presenting problem therefore being salvage of a live infant. It was further felt that this would be jeopardized if the forces of labor were allowed to impinge the fetus against the narrowed and very resistant outlet. The patient was consequently treated supportively.

The patient spontaneously entered into active labor Feb. 7, 1941, the membranes rupturing very shortly thereafter. The patient was taken to the operating room immediately and given 150 mg. of novocaine intrathecally. Low cervical transverse cesarean section was performed without technical difficulty. A normally developed viable male infant was delivered. Before the procedure was completed the blood pressure dropped to 70/40 notwithstanding two administrations of ¾ gr. of ephedrine, and extreme circulatory collapse with anoxemia and coma intervened from which the patient at no time aroused. Blood transfusions, stimulants, and nasal oxygen were employed to no avail. The patient died thirty hours following the section presenting throughout this interval the syndrome described above.

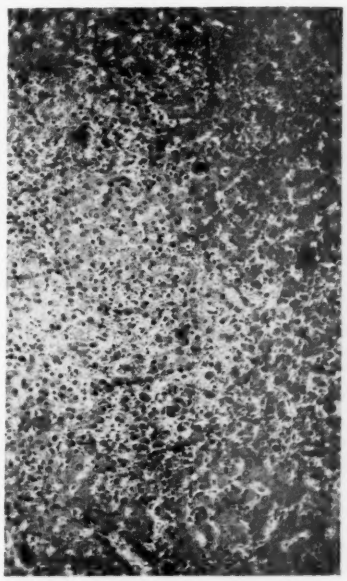

Fig. 1.

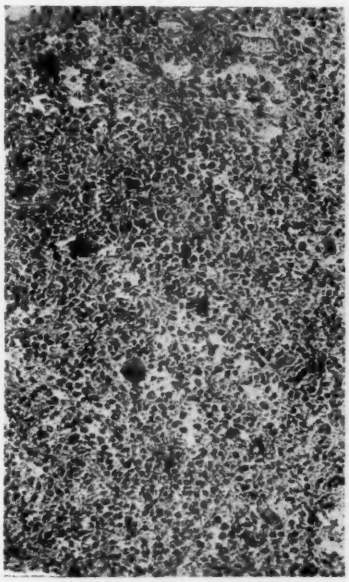

Fig. 2.

Fig. 1.—(No. 41-A-199.) Liver, ×55. *Diagnosis:* Early atrophy, red stage. Note loss of structure with necrosis of liver tissue and infiltration with polymorphonuclear leucocytes.

Fig. 2.—(No. 41-A-199.) Thigh, soft tissue, ×55. *Diagnosis:* Very cellular malignant sarcoma with little stroma and numerous tumor giant cells.

Autopsy.—Anatomic Diagnosis: Fibrosarcoma of the thigh; edema of the cervix and vagina; hypertrophy of the uterus (post partum one day); multiple splenic infarcts; acute yellow atrophy of liver.

The body was that of an extremely anemic, white, adult female. The breasts were enlarged, and on cut section showed a yellowish white material oozing from the prominent lobulated breast tissue. On the inner upper surface of the left thigh there was a fungating, ulcerating tumor mass. This was grayish red in appearance, soft in consistency, and it invaded the neighboring muscle. It showed marked evidence of necrosis and hemorrhage, but did not involve the bone. The peritoneum contained a small amount of clotted blood. There were a few areas in the bases of both lungs suggesting early bronchopneumonia. The spleen weighed 320 Gm. and showed multiple areas of recent infarcts. The liver weighed 1,700 Gm. It was somewhat soft in consistency, had

rounded edges, and was brownish yellow in color. On section the architecture was quite clearly delineated. There were numerous poorly defined, small, yellow zones within the liver parenchyma. The uterus was enlarged, the vagina and cervix edematous.

Microscopic examination showed evidence of bronchopneumonia. There were multiple areas of recent infarction in the spleen. The liver showed recent widespread areas of necrosis. These zones were scattered in a haphazard fashion throughout the liver parenchyma (Fig. 1). There was no evidence of regeneration of liver cells, and only very rare zones of hemorrhage. The liver cells in the regions of necrosis showed the disappearance of their nuclei and many of the cells were completely destroyed. The kidney showed fairly marked tubular degeneration. The uterus showed the characteristic changes one day post partum. Sections from the tumor showed a very cellular fibrosarcoma. Tumor giant cells were numerous. The nuclei of the cells were rich in chromatin, and showed many fine nucleoli. There was evidence of old and recent hemorrhage, and there was invasion and destruction of muscle (Fig. 2).

The tumor, a fibrosarcoma, showed no evidence of metastases. The liver atrophy was acute, widespread, and probably the immediate cause of death. The bronchopneumonia was an incidental and terminal finding.

CASE 2.—L. H. (No. 2092), colored female, aged 20 years, was first seen at the Cancer Hospital on Sept. 25, 1940, complaining of a tumefaction of the left buttock of five months' duration which first appeared following trauma. There had been increasing local pain which radiated down the posterior aspect of the lower extremity. Ambulation had been progressively impeded, and when seen at this time the patient was able to walk only with the aid of crutches. There had been a 22-pound weight loss since the tumor had first been noticed. There was a history of recent irregular menses, and the patient had been amenorrheic during the past two or three months. She had had one previous pregnancy which was normal.

Examination revealed a well-developed and well-nourished girl in apparent good general condition. On the left posteriorly, at the level of the gluteal fold, there was a firm, smooth, globular tumefaction, 12 cm. in diameter which felt fixed and remained immobile on rotation of femur. There was a marked limp due to pain and stiffness in the hip region. Examination further revealed evidence of a three and one-half months' pregnancy.

Routine laboratory procedures gave results within normal limits except for a moderate secondary anemia. The blood Kahn was negative. Roentgenogram of the hip revealed no bony changes, the tumefaction throwing a soft tissue shadow overlying the lateral aspect of the left hip joint and greater trochanter. Complete skeletal roentgenograms revealed no evidence of metastases. An approximate three to four months' fetal skeleton was visualized in the pelvis. The mass was biopsied at which time it was found to be encapsulated and, in part, cystic. The capsule was found to be inseparably attached to the capsule of the hip joint and to extend medially to the ischial spine from which it could not be separated. Histologic examination of the obtained tissue revealed a very cellular fibrosarcoma in which mitotic figures were infrequent (Fig. 3). It was felt that the only surgical approach of curative adequacy would

be hemipelvectomy. Because of disadvantages of this procedure and because of the marked cellularity of this tumor, x-radiation was favored.

Consequently the patient was given 2,000 roentgens x-radiation through each of four 10 × 15 cm. portals directed at the lesion at 50 cm. STD. (200 KV, 1 mm. copper, 1 mm. Al.). The patient stood the radiation well. She was discharged Nov. 15, 1940, at which time she was completely free of pain and was able to walk well. There was still minimal drainage through the biopsy wound.

When seen March 5, 1941, the tumor was observed to have markedly decreased in size. The incision was well healed. The fetus was found viable, in L.O.P., head floating.

On April 4, 1941, elsewhere, the patient spontaneously delivered a living female infant, which was apparently normal in every respect. The patient was seen in the clinic, along with her baby, on May 9, 1941. At this time palpation revealed the tumor to be firmer and slightly larger than on March 5, 1941. The patient was advised to enter the hospital for x-ray therapy to two new ports. She promised to enter in one week, but up to the present time, she has not returned, nor has the social service department been able to contact her.

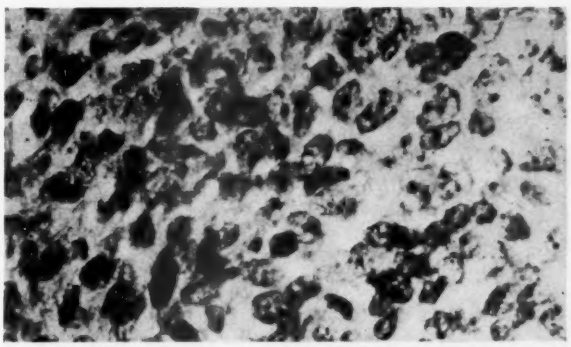

Fig. 3.—(No. 40-1468.) Buttock, soft tissue, ×240. *Diagnosis:* Fibrosarcoma. Very cellular, rapidly growing sarcoma with numerous mitotic figures.

DISCUSSION

In the first case, the tumor involved a large portion of the buttock near the pelvic outlet. It was obviously an inoperable lesion. The question arose as to whether x-radiation should be attempted. It was felt that this course of treatment would be purely palliative since fibrosarcomas do not, as a rule, respond well to x-radiation. Walther[4] reports 13 per cent of five-year cures with x-ray therapy, and states that the best results were with fibrosarcomas of the eyes, ears, oral cavity, mesopharynx, and mediastinum. Paterson[5] makes the statement that x-radiation is actually contraindicated for fibrosarcoma unless given as a palliative procedure. X-radiation of the tumor would have exposed the fetus to x-rays since the tumor extended into the pelvis. Mundell[6] has pointed out the dangers to the fetus of exposure to x-radiation. For these reasons it was decided to aim only at obtaining a live infant.

The second case represented a different problem. The patient presented herself earlier in pregnancy with a much more circumscribed tumor. The tumor, moreover, was situated so that x-radiation could be given without exposing the fetus to any of the primary beam, and to

very little scattered radiation. It was felt, therefore, that the mother deserved a thorough attempt at curative irradiation. Surprisingly enough, the tumor responded well, perhaps because of its marked cellularity.

One of the most unusual features of the first case is the acute yellow atrophy, which probably accounted for the patient's death. Rolleston[7] states that he has seen this disease only 13 times in thirty-four years, except when it was caused by specific poisons, such as arsphenamine, etc. This patient received no medication which could have been the etiologic factor. Barbiturates were not used, and the anesthesia was spinal. Apparently this was a case of acute yellow atrophy resulting from a combination of the pregnancy and the tumor. Until the cesarean section was done, however, there were no signs or symptoms of toxemia. Malignancy in itself, even when in the form of a rapidly growing sloughing tumor, does not cause acute yellow atrophy.

The diagnosis of acute yellow atrophy was not made before death, since the patient did not live long enough to develop jaundice.

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BASAL CELL CARCINOMA OF THE VULVA*

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THIS study concerns itself with basal cell carcinoma of the vulva, which is one of the rarer types of malignant neoplasms of the vulva. It is based on the study of 4 such cases occurring on the clinical service and private practice of Dr. Fred J. Taussig. The clinical cases were all observed since 1927 at The Barnard Free Skin and Cancer Hospital.

Following are the histories and findings in these cases of basal cell carcinoma of the vulva:

Case 1.—Mrs. M. S., a 72-year-old white woman, came to the Barnard Hospital Clinic because of an irritation on the left side of the vulva of twelve years' duration. She had 11 children and her menses ceased at the age of 57. This area of irritation ulcerated intermittently, causing an intense pruritus of the vulva. No bleeding was associated with this. The lesion began about the size of a small pea and continued to grow very slowly. Physical examination revealed a superficial ulcer about the circumference of a silver dollar at the upper angle of the left labium majus (Fig. 1). The ulcer involved the mucous membrane of the prepuce. The ulcer was not infiltrating in nature and the edges were hard and rolled. The base

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of the ulcer showed no attachment to the underlying tissue. A diagnosis of carcinoma of the vulva was made. There was no evidence of regional glandular involvement at this time. On Sept. 1, 1927, a vulvectomy was done. The lesion on the left upper half of the vulva was removed with a good surrounding margin of normal skin. The leucoplakic area over the labia minora was also removed from the level of the urethral meatus upwards.

Pathologic Examination (Dr. L. H. Jorstad).—"The specimen is that of an irregularly-shaped portion of skin from the vulva, measuring 4 by 7 cm. Part of the section is covered with mucous membrane and part with skin. At the mucocutaneous margin is an ulcerated area, irregular in shape, 1½ cm. in diameter. The edge of a portion of the ulcer is thickened and the remainder of the edge is smooth. The thickened edge is grayish white in color. The remainder of the ulcer is brownish gray in color and roughened. On section the whole area is made up of opalescent, fibrous tissue with no extension into the subcutaneous tissue. Microscopically, the section shows the edge of the ulcer which is sharply demarcated from the adjacent

Fig. 1.—Photograph of vulvar lesion (Case 1), involving the left labium majus and minus and prepuce.

skin. The epidermis at this point is thickened. At the base of this ulcerated area there are collections of epithelial cells which are basal in origin. There is no invasion of these cells below the subcutaneous tissue. There is a moderate amount of plasma and round cell infiltration present in the connective tissue." (Fig. 2.)

Diagnosis.—Basal cell carcinoma of the vulva.

Two years later the patient reported back to the hospital for observation, at which time several enlarged lymph nodes were felt in both inguinal regions. A bilateral Basset operation was done on Dec. 6, 1939, by Dr. Taussig. At the time of operation it was noted that there was only a slight lymphatic enlargement and only little evidence of malignant invasion on either the right or the left side. Pathologic examination of the lymph nodes showed nests of cells which were entirely different from the cells in the remaining portion of the gland. No definite mitotic figures were seen. These nests of cells were hypertrophic germinal centers. There was no disturbance in the normal architecture of the lymph glands. No evidence of malignancy was noted. The patient developed some fever on the first postoperative day and developed some moisture at the lung bases. She began to fibrillate and show signs of cardiac decompensation. She died on the tenth postoperative day. No post mortem was obtained.

CASE 2.—Mrs. R. A., a white married woman, aged 63 years, was treated at the Barnard Hospital in 1931 for multiple basal cell epitheliomas of the face and neck. In May, 1933, she developed several superficial ulcerative lesions on the mons veneris and on the left labium majus. They were treated by local excision and suture. Pathologically they showed small nests of cells composed of, for the most part, basal

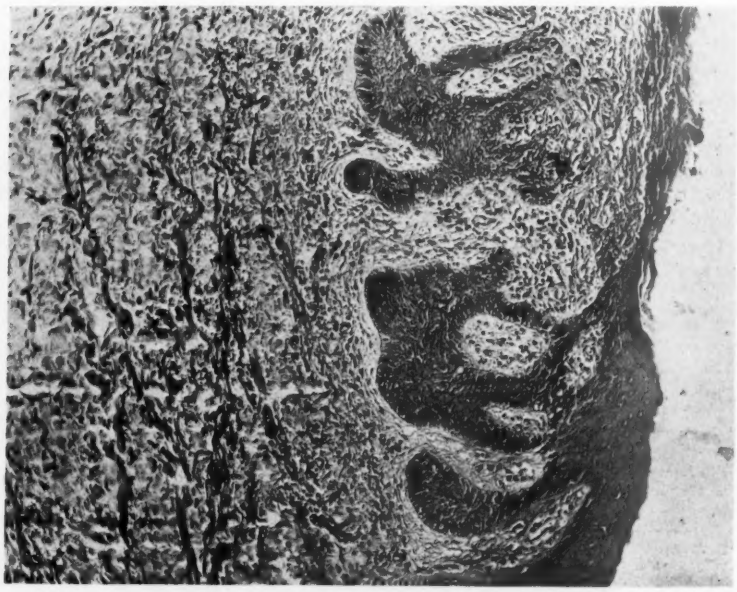

Fig. 2.—Section taken at margin of vulvar ulcer (Case 1), showing early basal cell carcinoma. There is some thickening of the epidermis present.

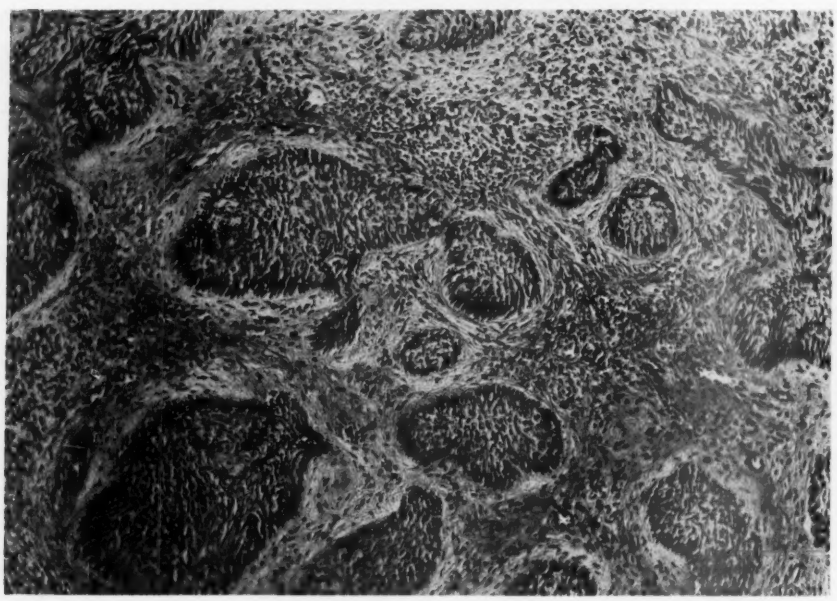

Fig. 3.—Showing cystic degeneration in the center of the islets of basal cells, giving rise to a cystic basal cell carcinoma (Case 2).

cells. These nests were compact, but occasionally showed some cystic degenerative areas in the center. The diagnosis was made of cystic basal cell carcinoma (Fig. 3). On Jan. 22, 1941, this patient was seen again and there was no evidence of recurrence.

CASE 3.—Mrs. G. K., a 42-year-old, white, married woman, came to the Barnard Hospital Clinic in July, 1932, complaining of a growth on the external genitalia. The lesion had been present for four years and had resulted in some bleeding. Physical examination was negative except for the pelvic findings. The patient showed an everting, hard nodule, red, with superficial leucoplakic spots on the nodule. The vulvar skin was normal. The left femoral glands were enlarged. The right-sided glands were not palpable. A diagnosis was made of carcinoma of the vulva (relatively benign). A bilateral Basset operation for removal of the inguinal-femoral lymph glands and a cautery vulvectomy were done. Microscopically the tissue showed cells grouped in masses of varying sizes and shapes. These cell

Fig. 4.—Showing ulcerated basal cell carcinoma involving the left labium majus and minus (Case 3).

masses lay in a bed of connective tissue. The cells were from the basal layer of the epithelium, and there was no tendency to invasion of the surrounding tissue. No metastases were found in the lymph glands. The patient's postoperative course was uneventful and she was discharged from the hospital in good condition. She was seen in September, 1940, at which time she showed no clinical evidence of recurrence.

CASE 4.—(Private case.) Mrs. G. A., a 63-year-old married white woman, complained of pruritus vulvae for the past twenty years and for the past three years noticed a growth in the left labium majus. She had used many different salves and ointments without any perceptible change. The lesion bled frequently and was tender at various times. It had not greatly increased in size in the past few years. She had no inguinal pain or adenopathy.

Physical Examination.—General physical examination was essentially negative except for a mild hypertension of 155/90. Pelvic examination revealed well-developed normal external genitalia. There was no clinical evidence of leucoplakia. Involving the left labium majus and part of the left labium minus was an ulcerated lesion about 4 by 6 cm., with a raised, pearly, hard border (Fig. 4). The base of

the ulcerated lesion was clean and showed no evidence of necrosis. The ulcer was not attached to the underlying tissue, and there did not seem to be any involvement of the adjacent skin. There were some small lymph glands palpable in the left groin. The left leg showed a marked dermatitis and scaling. There were many small varicosities in both lower extremities. A biopsy taken on Jan. 24, 1941, showed a basal cell carcinoma of the vulva. In view of the primary lesion and the palpable inguinal glands, a complete left vulvectomy was done with the cautery, and a left-sided Basset operation was done. The external iliac and obturator glands were found to be definitely enlarged and many small glands were found in the fat

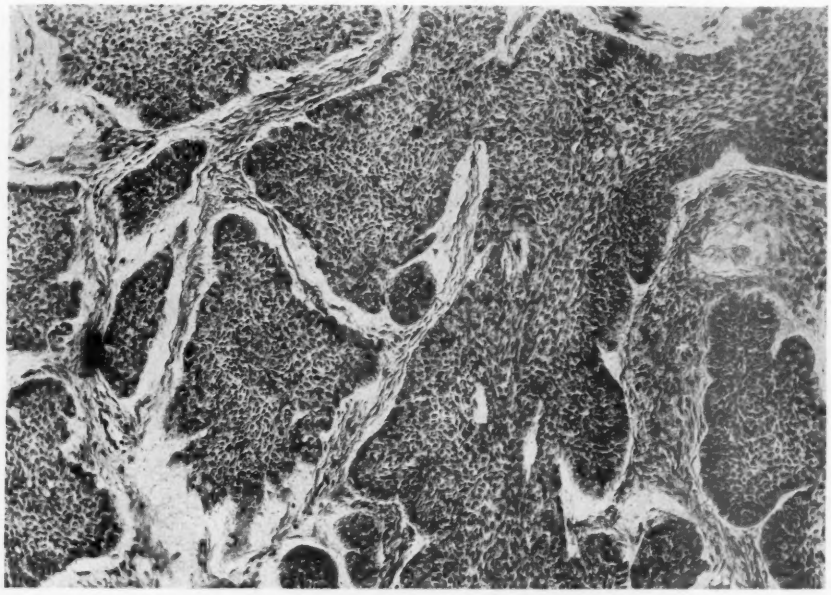

Fig. 5.—Microscopic picture of the lesion in Fig. 4, showing nests of malignant basal cells in a stroma of connective tissue.

in Scarpa's triangle. Microscopically the primary lesions showed nests of epithelial cells of typical basal cell type. These nests of cells were embedded in a dense connective tissue (Fig. 5). The lymph glands showed no sign of metastases. On the eighteenth postoperative day, the primary vulvar defect was skin grafted with pinch grafts and the patient was discharged from the hospital on the twenty-seventh postoperative day.

DISCUSSION

In general, these four cases represent the typical history of basal cell carcinoma. The history of a slow, painless growth, with recurrent episodes of ulceration and bleeding, terminating in an ulcerative lesion of varying size and involvement, is one common to basal cell carcinomas anywhere in the body. The absence of metastases in the regional lymph nodes is also a characteristic finding in these cases. These carcinomas are locally malignant and grow by extension, but they hardly ever metastasize. The enlargement of lymph nodes tributary to a basal cell carcinoma is usually due to secondary infection of the primary lesion, resulting in a hyperplasia of the lymph nodes. The follicles become hyperplastic and may be mistaken for areas of metastatic squamous cell carcinoma.

Each of these four cases presents the histologic picture of a basal cell carcinoma. The cells are derived from the basal layer of the epidermis. The cells stain darkly and the nucleus occupies the major portion of the cell, there being relatively little cytoplasm. In Fig. 2, one can see the basal layer of cells undergoing malignant degeneration at the margin of a rodent ulcer. These islets of cells are found in the dermis, and they do not invade the subcutaneous tissue. The other cases show more areas of more advanced malignant change. There is a total absence of keratinization and epithelial pearl formation in these cases. Fig. 3 shows evidence of cystic degeneration in the center of these nests of cells. Mitotic figures are found infrequently in these microscopic sections. These groups of cells do not show invasive tendencies.

Blair Bell and Datnow[1] found that malignant disease of the vulva occurs as squamous cell carcinoma in over 90 per cent of all cases. The other 10 per cent or less includes adenocarcinoma (Bartholin gland), sweat gland adenomas, basal cell carcinoma, melanoma, teratoma, sarcoma and endothelioma. In his analysis of 155 cases of vulvar carcinoma, Taussig[2] found 3 cases of melanoma originating about the labia and urethral meatus, 12 cases of periurethral cancer, 3 adenocarcinomas arising from Bartholin's gland, and the remaining carcinomas were of the squamous cell type. D. den Hoed[3] in analyzing the results obtained with the treatment of malignant tumors of the vagina, vulva, and urethra, found one case of basal cell carcinoma among 41 vulvar tumors, which gives an incidence of 2.5 per cent in this series. Göbel and Hamann[4] collected 69 cases of carcinoma of the vulva between 1915 and 1936. They found that vulvar carcinoma forms 3.5 per cent of all pelvic carcinomas in women. Of these 69 treated patients, 8 cases had recurrences. Among the remaining 61 cases, there were 9 cases of basal cell carcinoma and 44 cases of squamous cell carcinoma. This gives an incidence of 13 per cent basal cell carcinoma in this group. These investigators make note of the fact that the incidence of basal cell carcinoma in their series is higher than any other obtained in the five years previous to their report. Mosto and Radice,[5] reporting 23 primary malignant tumors of the vulva, found 21 carcinomas and 2 tumors of connective tissue origin. Of the 21 malignancies, one was glandular in origin, 19 were spinocellular in type, and one was a basal cell carcinoma. Folsome[6] found that basal cell carcinoma of the vulva is relatively rare. He reports 6 cases from the Michigan University Hospitals. Three patients had rodent ulcers elsewhere on the body, and in 2 cases there was more than one rodent ulcer on the vulva. These were treated by surgical extirpation. Claiborn and Holsinger[7] reported only 2 cases from the literature, and added one of their own.

In his monograph on diseases of the vulva, Taussig[8] divides carcinoma of the vulva into 3 groups:

1. Squamous cell carcinoma or cancroid, characterized by the formation of numerous epithelial pearls.

2. Medullary carcinoma springing from undifferentiated epithelial cells.

3. Adenocarcinomas arising from glandular structures about the external genitals.

He states that in point of frequency, the typical squamous cell cancers predominate and that outside of Bartholin's gland, adenocarcinoma of the vulva has hardly ever been recorded. No mention is made in this classification of basal cell carcinoma.

From a study of these 4 cases, it would seem that the treatment of basal cell carcinoma of the vulva need not be as radical as that of squamous cell carcinoma. A biopsy should be taken in all cases both from the edge and from the base of the ulcer to determine the histologic classification of the neoplasm. If the growth is basal cell in character, then a simple wide excision should be carried out without any extensive glandular removal. The Basset operation is not essential in all cases of basal cell carcinoma of the vulva. However, the patient should be observed every four to six months, and, if at any time a diagnosis of metastases to the regional lymph nodes is warranted, the Basset operation could be done with a reasonable chance of cure. Since none of these cases could be explained on a leucoplakic basis, it was not necessary to do a complete radical vulvectomy in each case. The dissection of the vulvar lesion should be carried down to the superficial fascia, since there is usually no involvement below the subcutaneous tissue. Radiation was not used in any of our cases.

SUMMARY

Four cases of basal cell carcinoma of the vulva are presented with case histories and treatment. One death is recorded due to postoperative cardiac failure and pulmonary edema following a Basset operation two years after the preliminary vulvectomy. At the time of the gland removal there was no evidence of any local recurrence. The other 3 patients are alive and well, eight years, nine years, and six months, respectively. All were treated by surgical extirpation without radiation. Three patients had a regional lymph gland removal, but in no case was there any evidence of any metastasis.

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HEMATOMA OF THE VAGINA ASSOCIATED WITH SEVERE PERINEAL TEARS

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VULVOVAGINAL hematoma is, in itself, a rare condition, but, combined with a complete rupture, unilaterally, of all the muscles of the pelvic floor with the exception of the gluteus maximus without a tear of the vaginal wall, has not, so far as the literature is available, been reported previously.

Mrs. E. B., aged 20 years, white (married to an Indian), para i, gravida ii, presented herself on March 7, 1940, for a prenatal examination. Her past history was essentially negative except for chicken pox at 6 years of age. The menstrual history was normal; menses began at 14, were regular, every twenty-eight to thirty days, lasting four days with little or no associated pain, and a moderate amount of discharge. There was occasionally a small amount of leucorrhea between periods. Venereal disease was denied. Her first child was born three years previously in an apparently normal delivery after a labor of fourteen hours. She was told by her physician that she suffered no tears and her postpartum course was smooth and uneventful.

Examination at this time revealed a well-developed, slender white woman, 62 inches tall (157.5 cm.), weighing 104 pounds (47.3 kg.), in good health, with a blood pressure of 118/70 mm. Pelvic measurements were a bitrochanteric distance of 32 cm., Beaudelocque's diameter of 19.5 cm., conjugate vera 11.0 cm., bispinous distance 11.0 cm., and a biischial diameter of 11.5 cm. The cervix was normal and pointed anteriorly. Hegar's sign was present and the uterus was 3 fingers above the symphysis pubis. The patient reported once monthly and the pregnancy progressed satisfactorily. In May, the patient had a thrush of the vagina which promptly cleared up after two treatments of soap and water scrubs, followed by application of a solution of gentian violet. She had a recurrence of moniliasis in July, 1940, which similarly responded to treatment. Urinalysis on all occasions presented normal findings. Her blood picture on July 2 was red blood count 4,750,800; hemoglobin (Sahli) 92 per cent; white blood count 7,300, of which 68 per cent were polymorphonuclear leucocytes, 22 per cent small lymphocytes, and 10 per cent large lymphocytes. Wassermann, Kahn, and Mantoux reactions were all negative.

On October 1, the patient reported for her last examination prior to delivery and stated she felt lightening two weeks previously. Nothing abnormal was found at this time. She entered the Holy Family Hospital on October 10 because of some irregular "labor pains." On October 11, at 5:00 P.M., she began to have pains fifteen minutes apart, lasting fifteen to twenty seconds. The pains increased in severity and intensity until about 8:00 P.M. when, upon examination, the cervix was completely dilated, the baby in R.O.A., and head deeply engaged. At 9:25 P.M., a living female child, weighing 7 pounds (3,180 Gm.), was

delivered normally. No tears of any kind were observed. Pituitrin, 0.5 c.c., was injected intramuscularly and the intact placenta came away spontaneously. There was no hemorrhage. Ten minutes after the extrusion of the placenta, the patient complained of a chill and seemed to go into a mild shock. This was believed to be due to the pituitrin and external heat was applied. At 10:10 (thirty-five minutes after the placenta was expressed), the patient complained of a severe "pressing and shooting" pain in the region of the coccyx and in the right buttock. There was a bulging in the right vulvovaginal wall and during the examination, this bulge gave way. The patient stated that she felt something give way but that she now felt all right. She was given 1/8 gr. of morphine subcutaneously. At 11:00 P.M. (fifty minutes later), she suddenly shrieked and stated that the pain returned, was more intense,

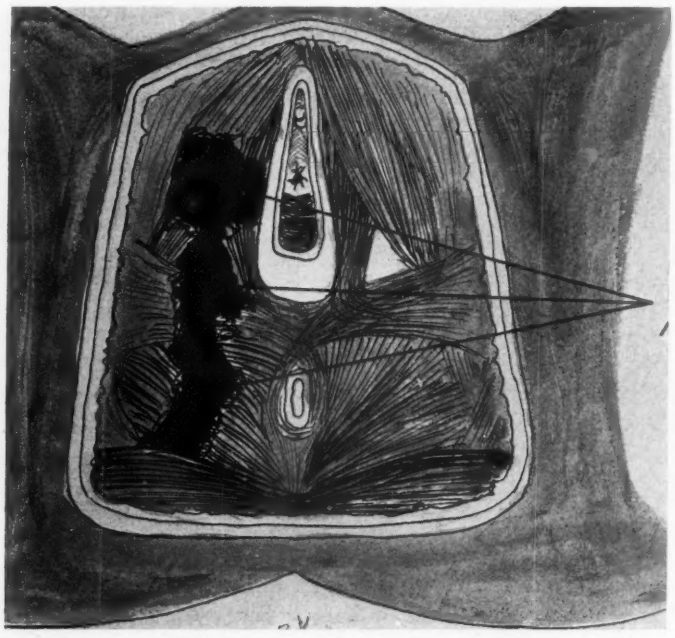

Fig. 1.—Semi-diagrammatic representation of rupture of all the muscles in the right perineum with the exception of the gluteus maximus. Note extent of rupture and hemorrhage, indicated by lines.

and that now, in addition, she had pain in the vagina. At this time, examination revealed the patient in shock and symptoms of an internal hemorrhage were present, i.e., anemia, restlessness, air hunger, rapid thready pulse of 140, numbness and coldness of the extremities, etc. There was a globular mass about the size of a large grapefruit in the right vaginal wall which was fluctuant, tense, purplish, and elastic. The mass was tender and the vaginal wall was glistening. Any movement of the right hip was excruciatingly painful. The fundus was firm, and there was no bleeding from the cervix.

Immediate surgery was done. When a longitudinal incision of the right vaginal wall was done, 1,500 to 1,800 c.c. of bright red blood and clots were evacuated. Hemorrhage was brisk. Hot packs were applied and bleeding points were ligated. After active bleeding was controlled,

torn muscle and fascia were observed in the cavity. The m. ischiocavernosus, the m. bulbocavernosus, the m. transversus perinei, and the m. levator ani were ruptured. The edges were ragged and thinned out. The sphincter ani and the m. gluteus maximus, the peritoneum, the urethra and the clitoris were intact. The vaginal wall, except for some thinning, appeared to be normal. Repair of the torn muscles and fascia was accomplished by mattress sutures with No. 0 twenty-day chromic gut after freshening and trimming the edges. The vaginal wall was sutured with No. 00 chromic and the expected cystocele was prophylactically corrected by a modified Graves operation for cystocele. An indwelling catheter was inserted and dry pads applied. Shock and blood loss were appropriately treated.

The postoperative course was uneventful except for a severe secondary anemia.

Blood counts were as follows:

10/16/40 red blood count 2,620,000 Hg (Sahli) 34%
10/20/40 red blood count 2,760,000 Hg (Sahli) 29%
10/23/40 red blood count 3,030,000 Hg (Sahli) 32%
10/26/40 red blood count 2,900,000 Hg (Sahli) 32%

The catheter was removed on the second day postoperatively, and the patient left the hospital sixteen days later.

Weekly follow-ups were done, and no evidence of scarring, cystocele, or rectocele was noted. Until the middle of November, there was some pain on defecation and on walking. The pain was localized in the right perineum and groin. But this too disappeared. On Nov. 14, 1940, the red blood corpuscles were 4,130,000 per c. mm.; hemoglobin 61 per cent. On Dec. 18, 1940, the red blood corpuscles were 4,690,000 and hemoglobin 96 per cent.

The patient, at the present writing, shows no abnormal external findings, but on deep palpation vaginally, an occasional mildly tender area may be demonstrated. There is no evidence of rectocele or cystocele. She has normal sexual relations and subjectively feels "better than ever."

COMMENT

It is interesting to note that a vulvovaginal hematoma developed a few minutes post partum. This hematoma, before and during examination, probably burrowed along fascial planes and the sensation of something giving way was due to rupture either of some of the perineal muscles or of fascia which may have been caused by purely mechanical pressure transmitted through the fluid contents of the hematoma. However, the manipulation during the examination was gentle and a more likely hypothesis would be that the hematoma burrowed through the fascial planes, separating and dissecting them from their normal close relationship. Moreover, while this hematoma was becoming progressively larger, ragged tears, thinning of muscle due to pressure of the increasing globular mass, and finally rupture of the fascial sheaths and muscle tissue ensued. After the initial rupture of portions of the muscles, these tears were further enlarged not only by the hematoma but by additional blood from the torn structures. During the process, there was a period free from pain but the recurrence of the pain occurred probably at the time when rupture of a partially torn muscle was completed. A great force is not necessary to tear muscles even as large as the levator ani, and probably the pressure exerted by a rapidly forming

hematoma was sufficient to do this. It will be observed that the clitoris and rectum were uninjured. This was presumably due to the fact that the hemorrhage did not ramify and burrow in those directions. Furthermore, these structures could easily be pushed out of the way by the mass of blood. The peritoneum was also untouched. It is likely that this may be due to the fact that the peritoneum is elastic, can stand much stretching and there are no relatively inelastic attachments. The gluteus maximus is too strong a structure to be torn in this manner.

SUMMARY

1. A case is presented of a vulvovaginal hematoma with severe internal perineal tears.

2. There was no apparent etiology for these conditions inasmuch as the delivery was normal, there were no apparent blood dyscrasias, labor was not prolonged, the baby was normal in size and weight, and there were no convulsive or violent movements during delivery.

3. There was an immediate hematoma followed by a latent period and finally true hematoma and tears.

4. Surgery was instituted on diagnosis with complete recovery.

5. A brief discussion of etiologic and surgical factors is presented.

DERMOID CYST IN THE UTERINE TUBE

A Case Report With a Review of the Literature

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ONLY twenty-four dermoid tumors of the uterine tube have been recorded; it, therefore, seems worth while to report an additional case. Only 4 of these are recorded in English, therefore the most salient features of all cases will be reported. It was not possible to obtain the report of Müller's case. Those of Prochownick and Ostreil are incompletely described. It is questionable whether the tumor described by Roberts is primarily tubal in origin. Previous authors have referred to the case reported by Robert Meyer; however, this is quite definitely a dermoid cyst of the ovary which encroached upon the uterine tube.

CASE REPORT

The patient, 33-year-old unmarried clerical worker, was admitted to the Beth Israel Hospital because of profuse vaginal bleeding (myomatous uterus). A supracervical hysterectomy and left salpingo-oophorectomy were performed. On gross examination the uterus, except for several large and small myomas, showed nothing unusual. The left ovary contained two corpora lutea. The tube was thin and slightly tortuous. Its fimbriated extremity was patent. Several pinhead-sized and larger thin-walled, clear cysts were situated on its posterior surface and in the broad ligament. At a distance of about 5 cm. from the tubal angle the tube was swollen, reaching a diameter of 1.5 cm., the tube then gradually tapering to normal thickness, which was reached about 3 cm. from the abdominal ostium. In the swollen area the whole thickness of the

tube appeared to be replaced by a unilocular cyst. The contents of the cyst after fixation were light grayish and gelatinous. No hairs were seen. The cyst wall easily separated into three layers, the middle of which was less than 1 mm. thick. The inside of the cyst was mostly smooth with some more or less distinct pits, grooves, and ridges. There was no communication on either side between the tube lumen and the cyst cavity. Cross sections of the tube on both sides of the cyst revealed nothing unusual.

Microscopic Examination.—Cross sections through the tube away from the swelling and long sections through the edges of the swelling did not reveal any abnormality or inflammation in the tube. The tube wall, especially the folds, was simply thinned out where it had been subjected to the pressure from the cyst. The thin-walled sac which fell out when the specimen was opened was lined with epithelium on its inner

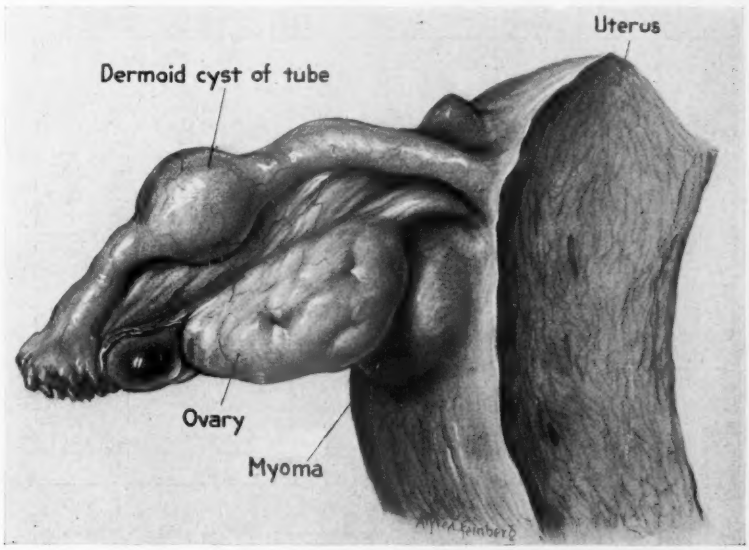

Fig. 1.—Gross specimen of tube and ovary. The swelling in the midportion of tube which represents the dermoid cyst has been bisected. The cyst at the lower edge is a large serosa cyst.

and its outer circumference. There were some folds and grooves. The epithelium at the outer circumference resembled tubal epithelium. It consisted of one layer, the cells were mostly cylindrical, many were cuboidal or flat. Cilia were seen occasionally on small groups of the cylindrical cells. There was little secretion. The inner epithelial lining was multilayered, ciliated throughout. There were occasional mucinous cells. The surface was smooth, only one fold was seen in the whole section. The stroma between these two layers was edematous. It consisted of connective tissue mostly, lymphoid foci (without centers), small and large areas of hyaline cartilage, nervous tissue, ganglion cells, and glands of bronchial type. Some of these glands had widely distended ducts. These small cysts were lined with flat epithelium, some of them empty, some filled with homogeneous material. In some sections the thin wall of the dermoid cyst could be studied in situ but no connection between tubal folds and the cyst wall could be found.

TABLE I. RECORDED CASES OF TUBAL DERMOID CYSTS

AUTHOR	DATE	AGE	GRAV.	HISTORY	SITE	SIZE	LOCATION	CONTENTS
Eden and Lockyer	1865	Not given				Large cocoon	Luminal, with a pedicle	Solid, with skin, sebaceous glands, hair, fibrous tissue, and areolar tissue
Scott	1883	55	iv	Prolapsed uterus 25 years. Menopause, 4 yr. Painful mass on right	Right	4 pounds	External. The tube formed the pedicle	Contained cheese, hair, and bone
Schouwmann	1890	43	xi	Pain in the R.L.Q. for 4 months	Right	Egg	In the lumen	Cystic, containing fat and hair
Pozzi	1896	33½	ii	Pain on left. Puerperal infection, 7 mo. Pregnancy in other tube	Left	----	In the lumen	Cystic, with cornified skin, sebaceous glands, sweat glands, hair, and adipose tissue
Jacobs	1899	48	0	Irreg. painful menses, 3 years. Painful mass on the left	Left	Orange	Outer third of the tube	Cystic, with sebaceous and calcareous matter. Author states microscopics showed conclusively dermoid of tube
Noto	1900	25	0	4 year history of painful enlarging tumor	Right	Orange	In the lumen	Cystic, containing tallow epithelium, sebaceous glands, endothelium, and round cells
Roberts Questionable case	1903	29	0	Amenorrhea, 4 months. Ruptured tubal pregnancy, right	Left	1¼ × ¾ in.	Attached to the fimbriated end	Solid, containing bone, cartilage connective tissue and epithelial necrotic mass.
Orthmann	1904	33	ii	Meno- and metrorrhagia. Pain in the R.L.Q. Pelvic adhesions	Right	9 × 3 × 4cm.	Attached to inside of tube by a thin pedicle	Cystic, with skin, hair, sebaceous and sweat glands, areolar tissue, smooth muscle, cartilage, bone, nervous tissue, giant cells, endothelium
Prochownick	1905	Not given			Bilateral	Presentation of gross specimen. No description found Both ovaries normal.		

Sneguireff	1905	–	Twins xiv	Dysmenorrhea. Palpable abdominal tumor	Right	---	In the lumen	Cystic, with epithelium, islands of cartilage, and glands
Potherat	1907	37	0	Pelvic adhesions	Bilateral	R—Orange L—Tangerine	In the lumen	No further description given
Stark	1912	38	0	Sterility. Dysmenorrhea	Bilateral	Tangerines	In the lumen	Cystic, with sebaceous matter, hairs, and plates of bone
Muglich	1912	Not given		Myoma uteri. Dysuria	Not given	---	Attached by a pedicle to the inner tube wall	Cystic, with greasy material and an "Embryomkörper"
Ostrcil	1913	Not given		Not given	Not given	Not given	----	Cystic, with hair and nervous tissue
Orthmann	1914	45	ii	Prolapsed uterus	Right	Hazelnut	In the lumen attached by a pedicle to the inner tube wall	Cystic, with derivatives of all three germinal layers
Ohno and Takaoka	1918	36	i	Pain, leucorrhea. Abdominal fullness for 10 yr.	Right	(cm.) 6.5 × 5.7 × 4.5	In the lumen. Isthmic portion of the tube	Cystic with pap, epithelium, hair, sebaceous and sweat glands, areolar tissue, cartilage, bone, nerve tissue, intestinal mucosa, giant cells, and smooth muscle and esophageal mucous membrane
Delannoy	1923	32	0	Fever and abdominal pain for 7 years. Bilateral pelvic tumors	Bilateral	R.15.5 × 13 × 12 cm. 470 Gm. L.15 × 5.5 × 5.5 cm. 275 Gm.	In the lumen. Outer third. Abdominal end	Cystic, with cartilage, bone smooth muscle, and sebaceous glands. Cystic, with 3 coats, desquamating pavement epithelium, cuboidal cells, sebaceous glands
Ulesko-Strogonowa	1925	Not given	0	Sterility. Meno- and metrorrhagia	Right	Egg	Attached to cornu by a pedicle formed by tube and ligament	Cystic, with skin, hair, bone, sebaceous glands, fat, giant cells and sievelike areas

TABLE I—CONT'D

AUTHOR	DATE	AGE	GRAV.	HISTORY	SITE	SIZE	LOCATION	CONTENTS
Aleev and Mamenkov	1925	48	iii	Abdominal pain for nine years	Right	Child's head	External. Attached to tube wall by a pedicle	Cystic with hair, balls, epithelium, sweat glands, Leiberkühn glands, intestinal lymph follicles, pancreas, cartilage, areolar tissue, thyroid, bone, and respiratory epithelium
Ronsisvalle	1927	46	0	Dysmenorrhea. Menorrhagia. Epigastric mass.	Bilateral	Lemon	In the lumen. The entire tube involved	Cystic, with pap, hair, skin, connective tissue, smooth muscle, areolar tissue, round cells, sievelike areas, simple tubular glands
Neumann	1927	36	i	Right tubal pregnancy mass on left side	Left	3.4 × 1 cm.	Attached by a pedicle to the inner wall of the tube	Cystic, with skin, sebaceous and sweat glands, fat and connective tissue, gland ducts lined with cylindric epithelium, round cells, giant cells
Aschheim	1932	42	0	Ovarian tumors, 4 years	Left	Finger	Attached by a pedicle to the inner wall of the tube	Solid, with skin, gland-like spaces lined with cylindric epithelium, mucous epithelium, cartilage, smooth muscle, adipose tissue, and round cells
Kraul	1938	40	–	Not given	Right	Child's head	External, with a pedicle	Solid, with skin, hair, smooth muscle, bone, cartilage, and connective tissue
Müller	1938	Not given		L. tubo-ovarian dermoid cyst. R. ovarian dermoid cyst	Right	Not given	Ampullary portion	Case details cannot be obtained
Aaron	1941	33	0	Meno- and metrorrhagia	Left	1.5 × 1.5 cm.	Intramural outer third of tube	Cystic, with skin, bronchial epithelium, cartilage, smooth muscle, nerve tissue, and round cells

COMMENT

It is beyond the scope of this paper to present the numerous theories concerning the genesis of teratomatous tumors and dermoid cysts. However, from a study of the recorded cases, as well as of our own, it is felt that the mode of development of these growths in the uterine tube may be demonstrated. As the Müllerian grooves in the urogenital fold become differentiated into the Müllerian ducts, a blastomere may become misplaced in the coelomic epithelium and is then incorporated in the tube wall to develop subsequently into a dermoid cyst or solid teratoma. It may reach intramural or grow inwards and perforate, or be attached by a pedicle to the inner wall of the tube; or else it may grow outward. Of the 23 adequately described cases the tumors were luminal in 15, of which 5 were pedunculated, 2 mural, and 8 external with a pedicle. Generally, the appearance was that of sactosalpinges, usually with adhesions to adjacent structures. In practically every instance the growths were situated in the middle or outer third of the tube. The cystic form is by far the commonest, in the ratio 20:6. No instance of malignancy is reported in the solid teratomas. Hairs were present in 12 cases. Their size varied from that of a hazelnut to a child's head. Since all the growths were incidental findings during the course of a gynecologic operation, statistics as to their frequency with respect to age are of little value. They have been found in patients from 25 to 55 years of age; 9 of these were parous, and 9 were nulliparous. In 3 cases there was a pregnancy in the opposite tube. They were more commonly unilateral than bilateral, in the ratio of 16:5, and occurred on the right side in ten instances, and on the left in six. It is interesting to note in this connection that dermoid cysts of the ovary seem to occur with equal frequency on either side, while teratomas of the testicle occur more frequently on the right. From the little material available at present, however, no conclusion may be drawn.

It is not easy to reconstruct in one's mind the arrangement and the way of formation of this dermoid in the tube. The thin sac which fell out when the swelling was incised consists of dermoid tissue and of tubal fold tissue. A similar layer, however, remained on the inside of the thinned-out tube wall after the aforementioned sac had been removed. We might assume that the dermoid cyst developed within a tubal fold replacing most of the tubal fold tissue by dermoid structures. While part of the dermoid formed a thin-walled round cyst, other parts infiltrated adjacent portions of tubal folds. Judging from the extreme thinning out of the tubal folds in the dermoid and in its neighborhood, it is not too difficult to conceive that one or several folds were completely destroyed by pressure atrophy, for instance, thus explaining the fact that one part of the dermoid was completely separated from the remainder.

SUMMARY

A case of a dermoid cyst in the uterine tube is presented.
The dermoid obviously originated within the tubal mucosa.

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BICORNUATE UTERUS, FULL-TERM PREGNANCY, AND PREMATURE SEPARATION OF CENTRAL PLACENTA PREVIA

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THIS patient presents a checkered obstetric history, including several pathologic labors and deliveries, in which a premature separation of a central placenta previa took place in a bicornuate uterus containing a full-term living baby in one horn.

The literature contains numerous reports of full-term pregnancies in double uteri; most of these are found in foreign publications and describe single cases. Frequently, the pregnancies terminated spontaneously with living babies. Beaver and Abbott[1] discuss normal pregnancies and deliveries in bicornuate uteri, with an extensive review of the literature. They collected numerous cases in which the pregnancy went to term. Falls[2] has frequently stressed the abnormal physiology of the uterus arcuatus.

In the patient herein described, the bicornuate uterus seems to have been an incidental occurrence which in no way hindered an extensive obstetric experience; however, its presence may have contributed to the existence of several pathologic labors and deliveries.

CASE REPORT

C. G., a 28-year-old Mexican female (Hospital No. 318533), entered the Los Angeles County General Hospital on Feb. 26, 1941, at 10 P.M. She stated that her pregnancy, now in the eighth month, had been entirely uneventful until the afternoon of admission, when she noticed slight bleeding followed by cramping pains.

Examination revealed an obese woman in good physical condition except for a blood pressure of 160/100. She had attended a suburban clinic for "chest trouble and bronchitis" for the preceding year, but a lung roentgenogram was negative. The blood and urine were negative.

Sterile vaginal palpation demonstrated an elongated cervix admitting a finger, moderate bleeding, and definite placental tissue directly over the internal os. Bleeding recurred after examination. The cervix and vagina were packed tightly with small moist cotton pledgets. This checked the bleeding.

A careful obstetric history-taking revealed the following bizarre career:

1931 Breech delivery of a living 8-pound baby.
1932 Breech delivery of a stillborn 7-pound baby.
1933 Spontaneous abortion at 4½ months.
1934 Transverse presentation, prolapsed hand, four-hour labor, delivery of a living 6-pound 7-ounce baby.
1936 Unattended delivery, one-hour labor, 6-pound baby.
1937 Transverse lie, mild pre-eclampsia, Voorhees' bag induction, version and extraction of a living 5-pound 3-ounce baby. The obstetric resident at the Los Angeles County General Hospital made a diagnosis of "double uterus" at this delivery.
1938 Spontaneous delivery, cephalic presentation, of 6-pound 8-ounce baby, complicated by unexplicable bleeding. Placenta previa or marginalis was suspected.
1939 Spontaneous abortion at 4 months, followed by curettage for postabortal bleeding.

Fig. 1.—Frontal section of bicornuate uterus, showing medial septum and placental site in right horn.

Laparotomy was immediately performed, using spinal anesthesia. The uterus was found to consist of two horns. The fetus occupied the right horn; the left horn was enlarged to the size of a four months' pregnancy. A low cervical incision was made through the uterine muscle transversely, and on exposure of the unruptured membranes, the placenta could be seen floating off its bed over the internal os. The membranes were then incised, the bloody amniotic fluid aspirated, and the fetus was delivered by podalic version. It was a stillborn female consistent in size with an eight months' pregnancy. Acting on the patient's preoperative request, sterilization was accomplished by extending the transverse uterine incision so as to perform a supracervical hysterectomy. She received a transfusion of 500 c.c. of citrated blood and was returned to the ward in good condition. She left the hospital on the eleventh day, after a completely uneventful postoperative course.

The uterus was bicornuate; the larger horn was 13 cm. and the smaller horn 12 cm. from the fundus to the point of amputation, as measured on the postoperative specimen. A thick 1½ cm. septum separated the two uterine cavities, and there was a common internal os and one cervix (Fig. 1). DeLee[3] calls this anomaly "uterus bicornis unicollis." The placenta was grossly normal, and a large retroplacental clot adhered to its maternal surface. Sections of the tissue showed hypertrophy and hyperplasia of the myometrium characteristic of pregnancy, with decidual endometrium in each horn.

SUMMARY

A patient with a history of several pathologic labors and deliveries was delivered by cesarean section of a full-term living infant in one horn of a bicornuate uterus in which there was premature separation of a central placenta previa.

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(1) *Beaver, M. G., and Abbott, K. H.:* California & West. Med. 47: 41, 1937. (2) *Falls, F. H.:* AM. J. OBST. & GYNEC. 38: 661, 1939. (3) *DeLee, J. P.:* Principles and Practise of Obstetrics, ed. 6, Philadelphia, W. B. Saunders Company, p. 561.

AN UNUSUAL BIRTH INJURY

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(From the Department of Obstetrics and Gynecology, University of Nebraska College of Medicine)

MUCH has been written of birth injuries and their management, but a brief survey of the literature and conversations with obstetricians of great experience fail to record a laceration similar to this case.

Mrs. S., nullipara, aged 30 years, was first seen in her second month of pregnancy. Her past history was essentially normal except for the fact that she was an habitual aborter. Examination revealed no abnormalities. Pelvic measurements were normal. Following examination the patient experienced some intermittent uterine contractions and spotting. For three months she was treated with massive doses of lipolutein and vitamin E. The remaining months of her pregnancy were entirely uneventful.

Labor began spontaneously seven days ahead of schedule. The first stage lasted thirteen hours and thirty minutes. Several hours after the onset of labor her pains became weak and irregular. This necessitated the administration of pituitrin, minims 1, 2, and 3, respectively, at thirty-minute intervals. Satisfactory analgesia was obtained with 10.5 gr. of sodium delvinal in divided doses over a nine-hour period. The membranes ruptured spontaneously at the end of the first stage. After forty-five minutes of the second stage, crowning occurred and the patient was then anesthetized with nitrous oxide and ether. The perineum and pelvic floor were "ironed out" and a midline episiotomy was performed; the upper margin of the incision extending approximately one inch above the hymenal ring. Forceps were applied to the head in L.O.A. position. Minimal traction was required for extraction. As the

forehead appeared over the perineum, the child's right hand suddenly protruded up to the elbow through the anus. This was immediately followed by the left hand which protruded up to the level of the wrist. Following delivery of the head and shoulders, the arms were easily drawn through the fistulous opening. With the completion of the third stage, a survey of the damage done revealed no extension of the medial episiotomy. The sphincter ani remained intact, as did the rectal wall for two inches above the anus and three-fourths of an inch above the level of the episiotomy.

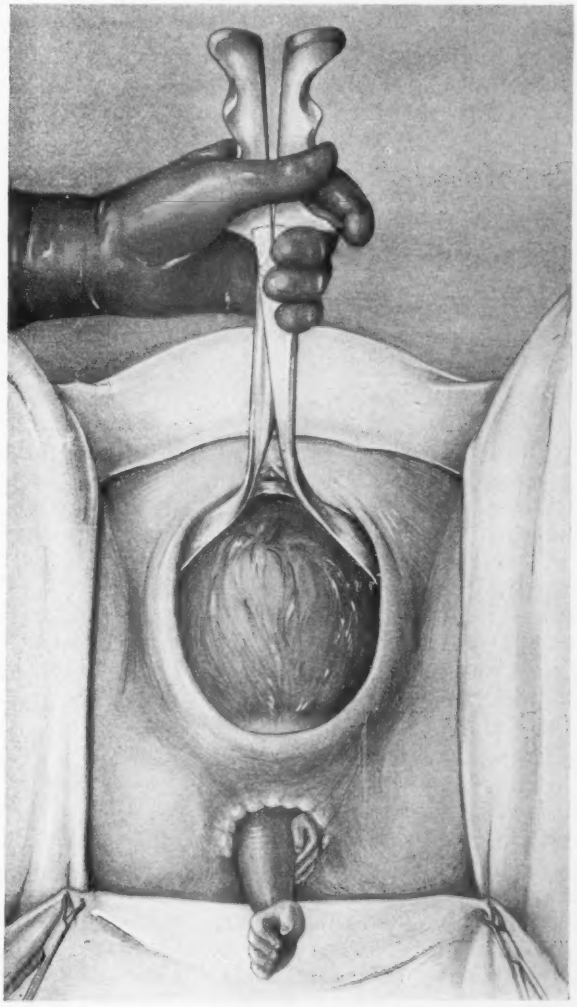

Fig. 1.

A complete laceration was effected by extending the episiotomy through the sphincter and rectal wall and into the fistulous opening. The rectum was closed in two layers; (1) a continuous submucous mattress suture of No. 0 plain catgut and (2) a continuous suture through the rectal muscle wall. The sphincter edges were approximated with

three interrupted 20 day No. 2 chromic gut. The vaginal wall was closed with interrupted No. 1 chromic gut. The perineal muscles were approximated with three interrupted chromic No. 1 sutures and the skin closed with a subcutaneous stitch of No. 1 catgut.

The baby was a healthy boy, weighing 6 pounds and 3¾ ounces. Occipitomental diameter was 13 cm.; occipitofrontal, 11 cm.; suboccipitofrontal, 10 cm.; suboccipitobregmatic, 9 cm.; biparietal, 8 cm.; bitemporal, 7 cm.; occipitomental circumference, 14½ cm.; shoulder diameter, 5½ inches.

The patient's puerperium was uneventful, and there was no incontinence of feces or gas. She left the hospital on the fifteenth post-partum day in excellent condition. The perineum had healed by primary intention. No extensive examination was made on discharge. Reports from the patient two months after delivery reveal that she retains perfect rectal control and has no perineal distress.

There is no satisfactory explanation for this unusual occurrence. The most logical one is that the attitude of the baby was responsible for the protrusion of the hands through the rectum and that, instead of the arms and hands being flexed across the thorax, the right finger tips were placed over the fetal chin and upon extension of the head the fingers pierced the rectovaginal septum. The left hand was apparently placed alongside the right forearm, as it appeared through the anus shortly after the right arm presented.

In the management of these cases, the major responsibility rests with the nursing staff for the meticulous aftercare so necessary for effective healing. The perineum was kept dry and clean. External antiseptic douches were given after each defecation and urination; the perineum was kept covered with a sterile pad. The perineum was painted with 4 per cent mercurochrome twice daily. No leg exercises were allowed for two weeks. Clear liquids only with no milk products were given for the first five days following which a low residue diet was given for the remainder of the lying-in period. Petrolagar, ounce 1, twice daily was begun on the second day in order to assure free movement of soft fecal matter. Retention enemas of petrolagar and water, ounces 1½ of each, were given on the third and fourth days. The patient left her bed on the tenth day.

There are two main schools of thought as to the aftercare of third degree lacerations; those who, like myself, believe in opening the bowels early and those who "lock them up" for the first week. This latter group believes best results are obtained by putting the intestinal tract at absolute rest, thus allowing time for primary healing. It has been my experience that best results are obtained by keeping the contents of the intestinal tract soft and unformed. Most complete tears are unpredictable and therefore the bowel, as a rule, has not been completely emptied before delivery. If peristalsis has been arrested, the fecal matter becomes dehydrated and presents itself in the form of hard and unpliable masses which, when passed on the seventh or eighth day, are liable to sever all suture lines. With experience in several large maternity hospitals, I have followed at least 25 complete lacerations handled by the above method. All but one case healed by primary union and that one developed a superficial infection which was controlled before the deeper structures were involved, and the patient left the hospital with perfect bowel control. No secondary repairs were required.

Society Transactions

OBSTETRICAL SOCIETY OF BOSTON

Meeting of October 21, 1941

The following paper was presented, by invitation:

The Vital Revolution. Mr. Guy Irving Burch, Director, Population Reference Bureau, Washington, D. C.

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MARCH 6, 1941

The following case reports and papers were presented:

Report of Jefferson Hospital Clinics. Dr. P. F. Williams and A. Behney.

Two Cases of Abdominal Pregnancy. Dr. Z. B. Newton.

The Relation of the Age of the Patient to Prognosis in Carcinoma of the Cervix. Dr. Pendleton Tompkins.

Vitamin A in Pregnancy. Dr. John C. Hirst and Robert E. Shoemaker. (For original article, see page 404, September, 1941, issue.)

MEETING OF APRIL 5, 1941

The following paper was presented:

The Theca Cone, the Pathmaker of the Ascending Graafian Follicle. Dr. Erwin O. Strassmann, Houston, Texas (by invitation).

MEETING OF MAY 1, 1941

The following papers were presented:

Presidential Address. Dr. Roy W. Mohler.

An Available Channel for Improved Obstetrics. Dr. Owen J. Toland.

The Etiology and Clinical Significance of Persistent Occipito-Posterior Positions. Dr. Paul O. Klingensmith.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Radiation Therapy

Schaefer and Huber: New Method of Roentgen Therapy in Climacteric Bleeding With Conservation of Ovaries, Strahlentherapie 64: 557, 1939.

The principles of the new method are the same as in radium treatment, i.e., destruction of the uterine mucosa with utmost protection of the ovaries. Radiation is given with the intracavitary x-ray tube used in cervical cancer, the anodal part of which can be introduced into the vagina.

Seven patients thus treated and observed for 1½ years after radiation are reported. In most instances bleeding ceased completely soon after treatment; in some cases mild bleeding returned once or twice, to be followed by amenorrhea. One case is mentioned, in which treatment failed to produce amenorrhea and the patient has been menstruating every four to five weeks. This case is instructive for two reasons: (1) It proves that the treatment does not endanger the ovarian function. (2) It establishes the optimal time for irradiation to prevent regeneration of the abraded mucosa. Whereas in all 7 cases radiation was given soon after the curettage, in this case it was given later, probably acting on the mucosa in its hyperplastic glandulocystic state.

As compared with radium, the new method offers the advantage of shorter duration of treatment (one hour by this method, twenty to forty hours with radium) and absence of reactive discharge, which occurs with radium therapy in 66 per cent. With the new method anesthesia is unnecessary, the cervix being sufficiently dilated after curettage for the passage of the aluminum cone.

J. P. GREENHILL.

Morrison, M. C.: Distribution of Radiation in Pervaginal Roentgen Therapy, Radiology 34: 451, 1940.

The author describes a method based upon the fact that the chief limiting factor to the administration of a cancericidal dose to any deep-seated tumor is the tolerance of the normal intervening structures, especially the skin. If the deep lesion can be exposed directly to a beam of x-rays without the beam having to traverse normal tissue a cancericidal dose can be safely administered. Carcinoma of the uterine cervix can be exposed through the vagina and treated as a superficial lesion. Daily doses of 450 r. are administered until a total of from 6,000 to 7,000 r. is delivered to the cervix in a period of about two weeks. The usual external roentgen series is given following the local treatment. When supplementary radium treatment is deemed advisable, it is administered as soon as subsidence of the radiation reaction in the vaginal canal permits. The author feels that pervaginal roentgen therapy has a slightly wider distribution of efficient cancericidal radiation than methods of radium application and has the further advantage that over-dosage of the canal region is avoided. In the pervaginal method no area more than 3 cm. from the uterine canal receives more than two threshold erythema doses, so that the bladder and rectum would appear to enjoy

relative protection by this method. He concludes that the daily continuous or interrupted series of pervaginal roentgen treatments would seem to fulfill adequately all requirements in the light of our present knowledge of this factor.

WILLIAM BERMAN.

Bouslog, J. S., and Evans, J. R.: Irradiation of Long Bones for Gynecologic Bleeding, Am. J. Roentgenol. 43: 871, 1940.

The writers encountered cases of functional uterine bleeding, intractable to ordinary forms of treatment, in which the only positive abnormal finding was a decreased platelet count. Because there were no other symptoms of purpura, they assumed that the diminution of platelets was due to a deficient formation in the bone marrow rather than to increased destruction by the reticulo-endothelial system (primarily the spleen). Therefore, irradiation of the long bones (100 roentgens to each of the long bones on several occasions) was instituted and the results were immediately successful: the bleeding ceased when the platelet count returned to normal. The disorder has been designated uterine purpura.

J. P. GREENHILL.

Arneson, A. N., and Hauptman, Harry: Radiation in the Treatment of Carcinoma of the Body of the Uterus, J. A. M. A. 116: 29, 1941.

This review of the subject indicates the authors' preference for a combined radiologic and surgical therapy. It is felt that hysterectomy alone is inadequate in the treatment of certain types of clinically operable patients, and that average results can be improved by combining radiation with surgery. In the treatment of any one case, certain factors such as the size of the uterus, the presence of infection, and downward extension of the tumor into the cervix should be taken into consideration. It is best to employ preoperative irradiation in all operable cases rather than attempt to individualize the treatment on the basis of the biopsy specimen. The important thing in irradiation is that in every instance an attempt must be made to deliver throughout the tumor-bearing region a dose believed to be adequate for control of the lesion in question. At the same time it is essential that an effort be made to decrease the discrepancy between the minimum dose delivered to some regions and the maximum falling on other points.

The authors feel that by increasing the greater number of irradiating sources, such as by the use of multiple capsules, the minimum tumor dose can be increased without resulting in extensive necrosis of adjacent tissue. They feel that Heyman's technique is one of the most effective methods at our disposal. If one contemplates or feels that infection is present, a preliminary course of x-rays should be used before the insertion of intrauterine radium. The best results are obtained from preoperative irradiation followed by hysterectomy.

WILLIAM BERMAN.

Kotz, J., and Parker, E.: Treatment of Functional Disorders of the Female by Radiation of the Pituitary Gland, South. M. J. 33: 832, 1940.

Two hundred and forty-three patients with functional gynecologic derangements, including various menstrual disturbances, sterility, the menopausal syndrome, and miscellaneous conditions, were treated by radiation of the pituitary gland in combination with organotherapy. They were followed for a period of from six months to nine years, averaging two years.

Most ovarian dysfunction is secondary to pituitary failure, the authors state, and therefore it is logical that therapy be directed toward the primary cause. The mode of action of pituitary irradiation is not known, but the end result seems to be that of stimulation. The statement is made that irradiaion is not harmful regardless of its effectiveness since regular menstrual cycles were not disturbed by the procedure. Amenorrhea was relieved in 56 per cent of the cases. Irregular periods were relieved or improved in 77 per cent of the patients. While estrogenic hormone therapy usually controls menopausal symptoms, pituitary irradiation

in addition may hasten the response and decrease the duration of treatment. Dysmenorrhea accompanying irregular periods responds well to this combined therapy.

The authors conclude that satisfactory results may be obtained in the treatment of functional menstrual irregularities by a combination of hormone therapy and pituitary irradiation. From their study they are unable to say which of the agents is the more important.

ARNOLD GOLDBERGER.

Rock, Bartlett, Gauld, and Rutherford: The Effect of Subcastrative Roentgen Therapy on Ovarian Physiology, Surg., Gynec. & Obst. **70**: 903, 1940.

Twenty-seven cases of menstrual abnormality, with and without associated sterility, are presented. The nature of flow has been evaluated by endometrial biopsy in an effort to determine whether flowing has been of the ovulatory or of the anovulatory type. Subcastrative dosages of x-ray have been employed in an effort to reestablish the normal balance of ovarian function. Endometrial specimens taken before and after x-ray treatment have been used in estimating the value of x-ray treatment to produce ovulation in those patients who do not ovulate or who have only occasional ovulatory cycles. No harmful effects from this treatment upon subsequent pregnancies have been found.

The results indicate that the use of subcastrative doses of roentgen rays is more effective than is the present endocrine treatment. Of the 22 cases of anovulatory flowing, or of infrequent ovulatory cycles, 12 had 3 or more ovulatory cycles following treatment. In 3 of these patients, pregnancy occurred within a short time following treatment.

Contrary to the experience of other investigators, no change after this dosage of x-ray was found in 5 patients with previous normal ovulatory cycles who had the associated complaints of sterility, dysmenorrhea, profuse menstruation, or too frequent menstruation. It is believed that x-ray treatment is indicated only when there is present definite ovarian dysfunction, specifically in those patients who habitually fail to ovulate, as shown by the absence of progestin effect on the endometrium.

Three doses, each of 50 to 60 r., are given over the ovaries of women under 35 years of age. Women older than this may suffer temporary or permanent cessation of follicular function.

It is the authors' opinion that x-ray treatment of the pituitary offers no additional therapeutic benefit.

To explain the good results it is necessary to postulate a destruction by x-ray of persisting mature follicles, thus allowing a new cycle of follicle development and maturation to take place.

WILLIAM C. HENSKE.

Costolow, William E.: Uterine Fibromyomas, J. A. M. A. **116**: 464, 1941.

The author reviews and re-emphasizes many well-known and established factors in the treatment of fibromyomas of the uterus. He stresses the importance of careful selection of cases for radiation therapy. Age is an important factor in choosing between radiation and surgery. Fortunately the majority of fibroids are in and close to the menopausal age which makes it somewhat easier for the physician to decide. There is very little evidence in favor of stirring up an acute pelvic cellulitis as a result of irradiating a fibroid in the presence of a chronic pelvic inflammatory condition. This condition, according to the author, could result more easily following a dilatation and curettage and radium application.

The author used deep roentgen therapy as well as radium and found the former more applicable in cases of large fibroids, because a large uterus screens out too much of the effect of radium rays on the ovaries.

No case of disability because of radiation menopause could be found in this series of cases, and only 10 patients out of 986 reported any change in "sex desire." Dyspareunia occurred in seven. In tumors the size of a three months' pregnancy or smaller, there was a reduction of the size of the uterus to normal in 84.3 per cent, and to only slightly enlarged in 93.5 per cent of the cases. In uteri

over the size of a 4 months' pregnancy the reduction incidence was reduced to 36.7 per cent. Large pedunculated fibroids show some tendency to degeneration, and should be operated upon if possible. Only 4 of the 986 patients developed carcinoma (3 fundal and 1 cervical), and it is suggested that radiation may have a protective effect in the prevention of malignancy.

WILLIAM BERMAN.

Chamberlin, Payne, and Stevens: Anuria Following Roentgen Therapy for Pelvic Tumors, Radiology **35:** 346, 1940.

Anuria, due to obstruction of both ureters, is a rare complication during roentgen therapy of tumors within the pelvis. Still rarer is the occurrence of bilateral symmetrical tumors, each involving the lower end of a ureter. The authors have been unable to find any other such case in the literature.

There is a dearth of literature dealing with anuria produced by tissue edema following irradiation therapy. Bugbee has reported 8 and Exley 2 instances of ureteral obstruction following radium therapy for carcinoma of the uterus. All of these, however, may be classified as late effects caused either by continued growth of the tumor, or by fibrosis and constriction due to irradiation therapy. Maintz has cited four instances in which anuria occurred as a complication of roentgen therapy early in the course of treatment for carcinoma of the uterus. His patients remained anuric as long as five days. He attributed the cessation of urinary excretion to swelling of the ureteral mucosa.

There seems to be little doubt that in the case reported by the authors irradiation produced sufficient edema in the tumor to cause a complete bilateral ureteral obstruction. This swelling was evident by rectal and vaginal examinations and also by the fact that the urinary secretion returned several days after roentgen therapy was stopped. In retrospect, it is evident that intravenous urography for the purpose of studying the exact condition of the urinary tract was indicated before roentgen therapy. Furthermore, it must be constantly borne in mind that relatively small doses of irradiation to such tumors may produce local swelling sufficient to obstruct the ureters when the margin of safety has already been reduced.

J. P. GREENHILL.

Duvergey and Duvergey: Fifteen Cases of Radionecrosis of the Bladder Following Radiation Therapy for Cancer of the Cervix, Compt. rend. Soc. franç de gynéc. **9:** 120, 1939.

Characteristically, radiation necrosis of the bladder following radium treatment of cancer of the cervix occurs long after the treatment is given. Usually between two and five years elapse, and in one of the authors' cases there was an interval of ten years. Clinically the symptoms are an intense cystitis with pollakiurea, tenesmus, pain, pyuria, and hematuria. In most cases, the impression is given that there is a recurrence of the cancer with invasion of the bladder wall. The way to be certain of the correct diagnosis is to take a biopsy. The usual seat of the bladder necrosis is in the region of the trigone at the base of the bladder at the bladder neck.

Radionecrosis of the bladder is the result of two factors. The first is an intense trophic disturbance caused by the radium and the second is infection. Because of an obliterating endarteritis, there is no vasomotor reaction to combat the infection.

The treatment of this condition consists of disinfection of the bladder by means of daily bladder irrigations with antiseptic solutions. If an ulcer is present it may have to be excised or coagulated. In cases of severe hemorrhage cystotomy may be necessary. Regardless of what is done, it must be remembered that complete cicatrization of the ulcer is a long process so one must have patience.

J. P. GREENHILL.

Item

American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in the various cities of the United States and Canada, on Saturday, January 3, 1942, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination will proceed automatically to the Part II examination held in June, 1942.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting at Atlantic City, N. J., in June, 1942, immediately prior to the annual meeting of the American Medical Association.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 1, 1942.

As previously announced in the Board booklet, this fiscal year (1941-1942) of the Board marks the close of the two groups of classification of applicants for examination. Thereafter, the Board will have only one classification of candidates, and all will be required to take the Part I examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Errata

In the article "Tattooing with Mercuric Sulfide for the Treatment of Intractable Pruritus Vulvae and Ani" by Dr. Robert Turell, in the August, 1941, issue of the JOURNAL, page 291, line 7 should read "with Dohi,[6]" instead of "with Aoki.[7]"

In the article "Lateral Pyocolpos, Double Uterus, Cervix and Vagina, with Absence of Left Kidney" by Dr. Max D. Mayer, in the November, 1941, issue of the JOURNAL, the position of Fig. 7, on page 903, should be reversed as to top and bottom.

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[1] Greene, R. R., J. Clin. Endocrin., 1, 559, July, 1941.

[2] Freed, S. Chas., Recent Progress in Estrogen Therapy, Meeting of the Illinois State Medical Soc., May 20, 1941, Chicago.

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